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RANGE OF NORMAL BLOOD PRESSURE

A STATISTICAL AND CLINICAL STUDY OF 11,383 PERSONS

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The determination of blood pressure is the third most important routine physiologic measurement that the modern physician uses with a fine degree of precision. While it does not carry an immediate purport in cases of acute illness as do the temperature and the pulse, yet for long range evaluation of the health of the average person it is far more significant. No other commonly used test gives such quick and reasonably exact information concerning life expectancy. With added information derived from the life history of the blood pressure and from mortality data a physician should be able to forecast the longevity or the general pathologic tendencies of many of his patients.

There has been a tendency lately to belittle the taking of blood pressure, but with the generally accepted realization that at least one fifth of the population is hypertensive and bears the stigma of an ominous prognosis, the blood pressure becomes a phenomenon of great moment. Heart disease accounts for more deaths in the United States than any other two causes,[1] and, as Cabot[2] stated: "Hypertension is more common than all other forms of heart disease put together." This

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The source material for this study was gathered from records accumulated during the past ten years by the Life Extension Examiners, Chicago; the West Side Y. W. C. A., Chicago; the Student Health Service of the University of Chicago, and the files of private practice. The statistical labor was performed with the aid of the Works Progress Administration.

1. (*a*) Dublin, L. I., and Lotka, A. J.: Length of Life: A Study of the Life Table, New York, The Ronald Press Company, 1936. (*b*) White, P. D.: Heart Disease, ed. 2, New York, The Macmillan Company, 1937.

2. Cabot, R.: Heart and Diseases, New York, W. B. Saunders Company, 1926.

is reflected in office practice, in which hypertension is the most common finding.[3]

Not only is the incidence of hypertension in the civilized population extremely high, but the nature of its morbid process is more widespread and deeply rooted than is generally believed by the average practitioner or even by the specialist in disorders of the heart. "Idiopathic" or "essential" hypertension, as is implied in its very definition, is supposed to be a syndrome unassociated with discoverable pathologic change. Some look on "essential" hypertension as a vague disease of the peripheral vascular bed. In reality it is a disease involving nearly all the viscera, especially the heart and kidneys. "High blood pressure is more frequently associated with beginning cardiovascular disease than any other discoverable sign," stated Cook.[4] Myocardial failure in most cases is due primarily to hypertension.[5] Fahr [5b] concluded that "nearly three-fourths of all so-called chronic myocarditis is due to primary hypertension." Levy [6] stated that hypertension is the most common single etiologic factor in coronary thrombosis. Fahr [5a] concluded that coronary sclerosis is present in 90 per cent of all patients who die of hypertension; similarly, Bell [7] found association of coronary sclerosis with hypertension in 75 per cent of cases. Roberts [8] stated: "The higher the tension the more we find diseased hearts." Hay [9] stated that "the usual termination of high blood pressure is cardiac defeat."

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3. (*a*) Foster, J. H.: The Practice of Medicine in China and New England with Observations on Hypertension, New England J. Med. **203**:1073, 1930. (*b*) Fisher, W. E.: Hypotension, M. J. Australia **1**:110, 1935. (*c*) Blackford, J. M., and Wilkinson, J. N.: Hypertension, Ann. Int. Med. **6**:54, 1933. (*d*) Lemann, I. I.: Effect of a Long Continued Subtropical Summer on High Blood Pressure, Am. J. Trop. Med. **12**:331, 1932. (*e*) Janeway, T. C.: A Clinical Study of Hypertensive Cardiovascular Disease, Arch. Int. Med. **12**:755 (Dec.) 1913. (*f*) Alvarez, W. C.; Wulzen, R., and Mahoney, L. J.: Blood Pressures in Fifteen Thousand University Freshmen, ibid. **32**:17 (July) 1923.

4. Cook, H. W., in discussion on Clark, C. P.: Theoretical Study of Blood Pressure and Its Relation to Heart Size, Body Surface Area and Metabolic Rate, Proc. A. Life Insur. M. Dir. America **20**:224, 1934.

5. (*a*) Fahr, G.: Heart in Hypertension, J. A. M. A. **105**:1396 (Nov. 2) 1935; (*b*) Hypertension Heart, Most Common Form of So-Called Chronic Myocarditis, ibid. **80**:981 (April 7) 1923; (*c*) Hypertension Heart, Am. J. M. Sc. **175**:453, 1928. (*d*) Christian, H. A.: Chronic Myocarditis, Tr. A. Am. Physicians **33**:67, 1918. (*e*) Janeway, T. C.: Note on Blood Pressure Changes, Proc. Soc. Exper. Biol. & Med. **6**:109, 1909. (*f*) Rogers, O. H., and Hunter, A.: Proc. A. Life Insur. M. Dir. America **10**:43, 1923.

6. Levy, R. L.: Diseases of Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936.

7. Bell, E. T.: Text Book of Pathology, ed. 3, Philadelphia, Lea & Febiger, 1938.

8. Roberts, S. R.: A Study of Hypotension, J. A. M. A. **79**:262 (July 22) 1922.

9. Hay, J.: The Significance of a Raised Blood Pressure, Brit. M. J. **2**:43, 1931.

That the kidneys are clinically associated with hypertension was known even before animal experimentation on the ischemic kidney.[10] Our own studies, to be published later, show this relation in respect to urinary findings. It is thus seen that hypertension is inseparable from cardiac and renal disease. In the light of these facts, "the control of hypertension is one of the outstanding challenges of today.[11]

While the cause, prevention and cure of disease are the ultimate justification for the study of any physiologic measurement, the workers in the laboratories of the basic medical sciences have yet another reason for coming to grips with the question of blood pressure. In studying the range of normal human physiologic measurements, such as the basal metabolic rate, blood chemistry values or electrocardiographic records, selection of normal healthy persons is necessary. Two criteria are used to select the "normal" healthy person: (1) his subjective state and (2) clinical measurements such as determinations of the pulse rate, temperature and blood pressure. The subjectively well state of a person, however, may be associated with morbidity, and one is often forced to fall back on simple clinical measurements. It is imperative that the physician know the levels at which these measures denote sound health.[12] The importance of finally settling the question of normal blood pressure to help unravel the mystery of hypertension is of the greatest moment; for the sake of correct understanding of normal physiology it is of equal importance.

It is in point that many authorities prefer not to commit themselves to definite levels of normal pressure, and some of those who do state normal levels show the uncertainty of their commitment by setting their lower limits of hypertension far above their own upper limits of normal pressure, thereby leaving a "no man's range." For example, Stieglitz [13] stated: "We may consider 140/90 mm. as the maximum normal systolic

10. Bell, E. T., and Clawson, B. J.: Primary (Essential) Hypertension: A Study of Four Hundred and Twenty Cases, Arch. Path. **5**:939 (June) 1928. Moritz, A. R.: Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, Am. J. Path. **13**:679, 1937. Riesman, D.: High Arterial Pressure, High Pressure Hypertrophy of the Heart, Am. J. M. Sc. **145**:487, 1913.

11. Major, R. W.: Chemical Factors Regulating Blood Pressure, Am. J. M. Sc. **183**:81, 1932.

12. This may be pointedly illustrated by a recent electrocardiographic study of the fourth lead (Shapley, R. A., and Hollaran, W. R.: The Four Lead Electrocardiogram in Two Hundred Normal Men and Women, Am. Heart J. **2**:325, 1936), in which the selection of normal persons was partially based on a blood pressure range which, as the present study will show, extended into hypertensive levels. Surely some of the subjects in that study of the fourth lead were false "normals."

13. Stieglitz, E. J.: Abnormal Arterial Tension, New York, National Medical Book Company, 1935.

pressure irrespective of age, and a systolic pressure of 150 mm. or more, diastolic of 95 mm. or more, constitutes hypertension." What status has the patient with a pressure of 146 systolic and 92 diastolic? There are great confusion and uncertainty about this important physiologic measurement. There is a range of 40 mm. between the lowest and the highest upper limit of normal, which, of course, yields a poor definition.[14] The normal has never been clearly and convincingly defined. Allen [15] stated that "the normal blood pressure of the total population, for different ages and sexes, is unknown." With this we agree.

We should like to discuss in some detail the factors which contribute to this uncertainty and discrepancy of authoritative opinion.

1. There are definite reasons for not accepting the levels obtained in the earlier work on blood pressure as normal physiologic levels. Most of the pioneer studies of blood pressure were done by and for insurance companies, and the tables are still accepted in all textbooks as the basis of blood pressure levels. Insurance statisticians did not set out to make contributions to human physiology; they were interested in the range of blood pressure in which they could establish a profitable insurance premium. Hunter,[16] actuary of the New York Life Insurance Company, stated:

> The investigations undertaken by the companies were primarily intended to assist them in determining which types of persons [also which levels of pressure] could safely be accepted for insurance at the regular rates of premium, which types should be charged an extra premium, and which should be declined. The purpose of the preparation of these statistics was not to excite public interest or curiosity, but for actual use in a great business.

2. Further, in medical research and among clinicians who deal every day with high and low pressures, the viewpoint has been taken that "if a subjectively-well and objectively-robust individual has a slightly elevated blood pressure, then slightly elevated blood pressures must be normal." Even today this type of reasoning is prevalent. However,

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14. Poulton, E. P.; Symonds, C. P., and others: Taylor's Practice of Medicine, ed. 15, Baltimore, William Wood & Company, 1936. Osler, W.: The Principles and Practice of Medicine, ed. 13, revised by H. A. Christian, New York, D. Appleton-Century Company, Inc., 1938. Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Co., Inc., 1937. Cecil, R. L.: A Textbook of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1937. Wetherby, M.: Comparison of Blood Pressures in Men and Women, Ann. Int. Med. **6**:755, 1933. Mosenthal, H. O.: The Diagnosis and Treatment of Variations in Blood Pressure and Nephritis, in Christian, H. A.: Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1929, vol. 7, p. 6.

15. Allen, E. V., in Musser, J. H.: Internal Medicine, ed. 3, Philadelphia, Lea & Febiger, 1938.

16. Hunter, A.: Can Insurance Experiences Be Applied to Lengthen Life? Proc. A. Life Insur. Pres. **8**:27, 1914.

a study over a period of years of many subjectively well and robust persons with slightly elevated pressures shows that they are not normal. This subject will be discussed in detail later.

3. All previous studies have included both normal and hypertensive pressures; these were averaged to arrive at a "normal" reading. It seems obvious that the abnormal blood pressures in the total population will distort the picture of the normal blood pressure averages. Some of the later workers spoke of this danger, but no author has ever attempted actually to separate normal from abnormal blood pressure groups in the statistical treatment of his series.

4. After the grossly hypertensive persons are excluded and there remains a sample of presumably normal persons, determination of the average—that most treacherous of statistical technics—is by no means the best statistical measure. The modal pressure would state more accurately the most common blood pressure.

5. When blood pressure levels are read by physicians, especially in insurance examinations, there is a tendency for the physician to round out his figure to keep it within the acceptable levels set for that year. In our own experience with the six physicians who have taken most of the records used in this study, it was noticed that as soon as pressures as low as 100 mm. were accepted as normal there was an increased incidence of these low readings, and when further revision reduced the lower limit of normal systolic blood pressure to 90 mm. still lower readings were recorded. This is not an evidence of intellectual dishonesty; it means merely that few physicians will deny a person insurance because of a reading of 5 mm. or so of mercury; nor in a routine periodic examination does a physician wish to excite the patient by the ominous words "low blood pressure" and the false pathologic implications they carry. He gives the patient the benefit of the doubt and so forever removes from statistical tables readings that are pertinent to the understanding of true normal blood pressure.

6. Another source of error noted by practically all workers is the tendency on the part of physicians to round out their manometer readings to the nearest unit of 10.

7. The "normal" is sometimes defined as the "most common"; however, even the most common blood pressure need not be a normal blood pressure, for purely statistical interpretation does not necessarily reveal true physiologic levels. To understand the real meaning of vascular tension one must augment statistical data with life histories of blood pressure and with mortality data.

8. Even after all these statistical and clinical precautions are taken, one is not justified in assuming that the range of blood pressure so obtained is the true normal physiologic measure for the human being.

It must be remembered that the studies are, in the main, studies of confined, sedentary persons with faulty hygienic habits. One must interpret such studies in terms of "normal" living.

The interplay of all these errors, especially the inclusion of the abnormally high readings of hypertensive persons in values for the total groups studied, has resulted in blood pressure levels that are obviously too high. Many clinicians with even a limited experience question these levels, and this has had its effect on studies of blood pressure in the last two decades. A chronologic study of the outstanding contributions on blood pressure proves this.[17] In the last quarter of a century the level of normal pressures has been persistently lowered. This shift of levels was apparent twenty-five years ago and was recognized by Janeway.[3e] Fifteen years ago it was mentioned by Alvarez.[3f] In the recent literature occasional statements have appeared which fix normal blood pressure at levels which in 1910 would have been considered to indicate hypotension. Is this declining standard due to a drop in the blood pressure of normal persons, or are ideas concerning normal levels changing? The collected data of various authors on blood pressure measurements show the latter to be true, though the change in ideas is, to be sure, very slow. Through years of application, the old formula "100 plus your age" has become a deeply rooted conception, so much so that even otherwise competent statistical research has been colored by this established idea.

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17. (*a*) Woley, H. P.: The Normal Variation of the Systolic Blood-Pressure: A Study of One Thousand Cases, J. A. M. A. **55**:121 (July 9) 1910. (*b*) Norris, G. W.: Blood Pressure, Philadelphia, Lea & Febiger, 1916. (*c*) Osborne, O. T.: Disturbances of the Heart, ed. 3, Chicago, American Medical Association Press, 1925. (*d*) Granger, A. S.: Present Conception of Essential Hypertension J. A. M. A. **93**:819 (Sept. 14) 1929. (*e*) Alvarez, W. C., and Stanley, L. L.: Blood Pressure in Six Thousand Prisoners and Four Hundred Prison Guards: Statistical Analysis, Arch. Int. Med. **46**:17 (July) 1930. (*f*) Fishberg, A. M.: Hypertension and Nephritis, ed. 3, Philadelphia, Lea & Febiger, 1934. (*g*) Huber, E. G.: Systolic and Diastolic Blood Pressure in Healthy Men, Human Biol. **5**:542, 1933. (*h*) Wright, S.: Applied Physiology, London, Oxford University Press, 1934. (*i*) Mosenthal, H. O.: Normal Blood Pressure, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1931, vol. 12, p. 644. (*j*) Dingman, H. W.: Selection of Risks for Life Insurance, Health Insurance, Accident Insurance, Cincinnati, National Underwriter Co., 1935. (*k*) Corwin, J., and Herrick, W. W.: Relation of Hypertensive Toxemia of Pregnancy to Chronic Cardiovascular Disease, J. A. M. A. **88**:457 (Feb. 12) 1927. (*l*) MacKenzie, L. F., and Wells, P. V.: On The Interpretation of Blood Pressure, Proc. A. Life Insur. M. Dir. America **19**:89, 1932; New York, Press of Recording and Statistical Corporation, 1933. (*m*) Wiggers, C. J.: Physiology in Health and Disease, Philadelphia, Lea & Febiger, 1934. (*n*) Dally, J. F. H.: High Blood Pressure, in Rolleston, H.: The British Encyclopaedia of Medical Practice, London, Butterworth & Co., Ltd., 1936, vol. 2, p. 503. (*o*) Palmer, J. H.: Blood Pressure in the Years Following Recovery from Coronary Thrombosis, Lancet **1**:735, 1937.

Finally, no previous study has incorporated the continuous records of blood pressure over long spans of time, nor have conclusions been checked with mortality data. These two additional phases of analysis are indispensable to an intelligent understanding of the subject. They add a dynamic interpretation to what has been thus far merely a static study.

STATISTICAL ANALYSIS OF THE TOTAL GROUP

To arrive at a better solution of the problem of the range of normal blood pressure we undertook an exhaustive statistical study of 7,478 men and 3,405 women selected at random. All lived in or around Chicago and were of that economic class which can afford an insurance policy of $1,000 or more. The majority came for a routine periodic examination given gratis by their insurance company. Most of the examinees had either no complaints or minor ones.

In selection of any source material for a study of normal blood pressure the sample should be truly representative of the total population in respect to all variables (age, sex, height, weight and occupation). Given a representative sample, the physical examination must also be rigidly standardized. Most samples hitherto studied have not met one or another of these requirements. Generally, insurance statistics have represented examinations made under a variety of conditions.[18] Other studies have been made on select groups of army men, prisoners or students. Some have even included patients in hospitals.

Our group, while based on accepted risks for life insurance companies, represents for the most part persons examined long after the original policy examination and, according to Dublin,[19] of the Metropolitan Life Insurance Company, is therefore more generally in accordance with a random sample of the population. In general, then, our group comes close to being a typical portion of all age groups between 20 and 70, includes both sexes and was taken under conditions of general health comparable to those of any random group in the total population. It must be remembered, however that the group was composed for the most part of urban men and women who were relatively sedentary in their occupation and recreation.[20]

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18. Wright and his associates presented an illuminating description of the force of possible error in blood pressure readings by different physicians (Wright, I. S.; Schneider, R. F., and Ungerleider, H. E.: Factors of Error in Blood Pressure Readings: Survey of Methods of Teaching and Interpretation, Am. Heart J. **16**:469, 1938). See also Diehl, H. S., and Lees, H. D.: The Variability of Blood Pressure: Study of Systolic Pressure at Five Minute Intervals, Arch. Int. Med. **44**:229 (Aug.) 1929.

19. Personal communication to the authors, Feb. 9, 1937.

20. The thirty minute examinations of the persons included in our study were standardized as far as possible. All blood pressure readings were taken with the

(Footnote continued on next page)

For 7,478 men the arithmetic average, or mean systolic blood pressure was found to be 121 mm. About two thirds of the men had blood pressures within a range of 17 mm. of the average (designated as the standard deviation of the mean). Generally, then, the blood pressure of men ranged from 104 to 138 mm. In a similar sample of 3,405 women the average systolic pressure was 117 ± 10.8 mm. Hence, the systolic pressure of most women ranged from 106 to 128 mm. The average diastolic pressure for men was 74.4 mm., with a standard deviation of 10.5 mm. The average diastolic pressure for women was 71 ± 11.5 mm. For the most part, then, diastolic pressure for men ranged from 64 to 85 mm., and for women, from 60 to 83 mm.

If one works only with a broad, unselected sample, it is better to determine where the values congregate than to use averages. To state it in statistical terms: What is the modal pressure of these groups? Most of the values for men were congregated around 115 mm. systolic and 71 mm. diastolic (table 1), and those for women were most frequently grouped around 113 mm. systolic and 70 mm. diastolic. We consider these modal pressures more significant than the mean or average readings which are so generally cited.

Almost two thirds of all blood pressures were below 125 systolic and 80 diastolic. This is a more important statement than the modal or average figure, because, as we shall show, the lower levels are highly desirable. Comparison of the mean and the modal systolic pressure indicates strongly that the abnormally high pressures effect a considerable distortion of the average figure; the "average" therefore, cannot rightly be interpreted as "normal" (chart 1). Because this distortion falls principally in the upper age groups, the false impression prevails

subject sitting and on the left arm with a mercury manometer. A total of six physicians made all of the examinations abstracted in the 10,883 cases of our total group study. Most of the women were examined by a woman physician. Each physician was acquainted with the technic of the others, and in instances of interestingly high or low readings the physicians checked each other's work. In all cases of abnormally high or low readings a reading was repeated as a check at the end of the examination to discount emotional or transitory rises, the lowest readings being recorded. In some cases three or more readings were necessary. The auscultatory method, with Bowles's bell diaphragm stethoscope, was used throughout, though occasionally the tactile method was used as a check.

The diastolic reading was made at the commonly accepted fourth phase—at the end of the loudest sound. If the rate of deflation is too rapid the reading may be distorted, and usually the examiner catches the reading too high. Deflation should be rather slow. A value of 0 diastolic should never be recorded; however, when the diastolic sound is faint and difficult to read or when some sounds continue to be audible down to or near zero, the flat diaphragm of the stethoscope should be inserted under the lower edge of the cuff, along the course of the brachial artery, on the medial aspect of the lower third of the upper part of the arm. This usually clarifies the diastolic sounds, as well as the systolic.

TABLE 1.—*Relation of Age to Blood Pressure in 7,478 Males and 3,405 Females (Total Group)*

Men	Age Groups															
	Under 15	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80 and Over	All Ages
Number of cases	17	96	539	1,113	1,202	1,185	1,064	903	550	393	227	116	48	16	9	7,478
Percentage of total	0.2	1.3	7.2	14.9	16.1	15.8	14.2	12.1	7.4	5.3	3.0	1.6	0.6	0.2	0.1	100.0
Systolic pressure, mm.																
Mean	98.7	118.3	119.0	118.5	117.5	117.6	120.1	122.7	125.6	129.6	131.7	138.6	137.2	154.4	147.5	121.0
Modal	92.5	123.4	120.8	117.3	113.6	112.5	118.3	114.9	113.9	122.3	122.2	124.2	130.6	126.2	140.0	115.9
Percentage under 100	64.7	5.2	4.6	5.0	5.2	5.7	6.3	5.0	4.7	4.8	4.0	2.6	4.2	...	...	5.3
Percentage under 120	94.1	50.0	51.0	53.9	58.6	50.2	51.1	49.6	44.3	37.4	31.2	23.3	29.2	18.8	11.1	51.3
Percentage over 140	....	3.1	5.6	4.8	4.6	5.1	9.2	1.5	2.2	25.4	29.1	43.9	43.8	62.5	55.6	10.8
Diastolic pressure, mm.																
Mean	56.0	68.2	70.8	72.0	72.7	74.0	75.7	77.0	77.3	78.2	77.5	76.7	77.3	80.0	87.5	74.4
Modal	50.6	67.0	72.3	72.0	71.8	71.6	71.5	70.7	70.4	72.5	69.4	69.5	69.5	85.1	72.5	71.1
Percentage under 60	64.7	1.1	7.8	6.5	5.1	3.8	3.1	3.4	3.5	2.3	4.0	7.0	4.2	12.5	....	4.8
Percentage under 80	100.0	91.0	82.9	79.7	79.8	73.3	65.5	61.4	60.2	59.0	60.3	63.8	60.4	43.8	44.4	66.6
Percentage over 90	.....	1.0	2.0	3.1	3.4	5.0	8.0	11.9	12.8	13.9	11.1	16.4	12.5	37.5	11.1	7.3
Women																
Number of cases	12	80	302	531	609	589	495	349	201	141	71	35	8	2	....	3,405
Percentage of total	0.4	2.4	8.9	15.6	17.9	16.7	14.5	10.2	5.9	4.1	2.1	1.0	0.2	0.1	....	100.0
Systolic pressure, mm.																
Mean	106.7	107.4	108.4	110.2	111.6	114.4	119.0	125.4	125.8	138.2	142.8	145.9	136.9	167.5	....	117.0
Modal	101.6	109.8	106.6	110.5	111.3	112.2	112.7	114.9	112.3	116.1	126.9	139.6	.....	.....	....	113.4
Percentage under 100	33.3	21.3	22.8	22.1	19.8	15.5	14.7	8.3	7.0	5.0	5.6	2.9	12.5	.....	....	15.8
Percentage under 120	83.3	88.9	84.1	79.2	80.3	69.2	58.2	45.6	46.8	34.0	21.1	20.0	25.0	.....	....	65.1
Percentage over 140	....	....	....	1.5	1.8	5.4	12.3	20.9	21.4	37.6	46.5	57.2	71.4	50.0	....	10.0
Diastolic pressure, mm.																
Mean	64.2	63.9	65.4	67.1	69.0	70.7	73.2	75.4	75.7	79.0	81.0	80.2	75.0	80.0	....	71.0
Modal	55.5	61.5	62.7	64.1	67.5	70.7	71.1	70.6	70.6	76.0	82.5	81.4	....	....	....	70.1
Percentage under 60	41.7	31.3	25.2	21.5	17.4	11.4	11.5	7.2	5.5	7.1	5.6	5.7	....	....	....	14.7
Percentage under 80	83.3	95.0	95.0	90.0	83.3	82.4	71.3	65.3	66.2	56.0	43.7	48.6	75.0	50.0	....	78.6
Percentage over 90	....	....	....	0.9	3.0	5.1	9.1	11.5	10.9	19.9	22.5	20.0	12.5	50.0	....	6.3

that "normal" blood pressure rises with age. The coefficient of correlation of age and systolic pressure for the total group was 0.14 ± 0.01 for men and 0.41 ± 0.01 for women; that of age and diastolic pressure was 0.22 ± 0.01 for men and 0.35 ± 0.01 for women. Neither of the correlations for men is significant of a rise in blood pressure with age. The slight significance of the correlation for women will be discussed later.

Since our total group of 10,883 persons, like every other group previously analyzed, contains this conglomerate of normal and hypertensive persons, it is not justifiable to draw conclusions concerning normal levels of blood pressure from such a sample. One must devise some method of roughly separating the pathologic from the normal pressures before the group is subjected to an extensive statistical

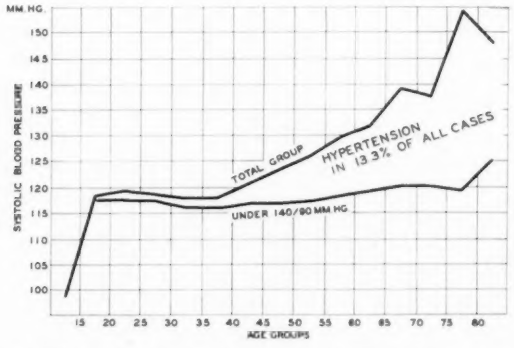

Chart 1.—Effect of hypertension on the blood pressure curve. The average systolic pressure of the total group of 7,478 men rises with age; however, when the obviously hypertensive persons (over 140 systolic and 90 diastolic) are excluded, the average blood pressure of the 6,485 men with blood pressures below this level does not rise with age.

analysis. This we shall do in the next section of the paper. We cannot yet say, therefore, what "normal" blood pressure should be from this statistical study of our total group of 10,883 persons.

DELIMITED GROUP

(Pressure of 140/90 and Over Excluded)

Study of the distribution of presumably normal blood pressures necessitates drawing an arbitrary line between normal blood pressure and hypertension at a point which is compatible with accepted opinion and at the same time overcomes the inherent errors of the total group study. There is accumulating a large body of evidence, such as statistical

and clinical studies and mortality rates, that demand the recognition of a level of 140 mm. systolic and 90 mm. diastolic at least (as will be shown even this is much too high) beyond which the pressures are definitely hypertensive. During the last ten years an ever increasing number of authorities in this field have placed 140 mm. as the upper limit of normal systolic pressure. Allen [15] stated: "A systolic pressure of more than 140 mm. should be regarded as abnormal." Alvarez [17e] stated: " A pressure of 140 mm. is just as abnormal in an old man as in a young one." Huber [17g] stated: "A systolic pressure of 140 mm. or more . . . is regarded as above normal." Faught [21] stated: "A pressure above 140 mm. is unsafe at any age." Diehl and Sutherland [22] also used 140 mm. as the upper limit of normal, as have many others. Mortality studies have shown conclusively that pressures above 140 mm. are definitely associated with a sharp increase in mortality.[23] For the purposes of this study we have, arbitrarily to be sure, used a pressure of 140 mm. as the dividing line above which an abnormal systolic blood pressure definitely exists.[24]

There seems recently to be an equal consensus that the upper limit of normal diastolic blood pressure should be placed at 90 mm. (In our own selection 93 per cent of the readings were below 90 mm.) It seems apparent that a higher level is in complete discord with any rational view of diastolic pressure. We have arbitrarily chosen 90 mm., therefore as the upper normal diastolic pressure for the selection of our delimited group. The delimited group contains only those persons whose blood pressure was under 140 mm. systolic and 90 mm. diastolic.

There are other reasons for selecting this group for detailed analysis. In order to orientate ourselves as to which range of blood pressures effected most of the distortion of the mean in the total group, we serially discarded the upper brackets of the higher pressures and noted the effect on the age–blood pressure curve. The rise with age that is

21. Faught, F. A.: Simple Method for Determining Normal Average Systolic Blood Pressure at Any Age, M. J. & Rec. **135**:160, 1932.

22. Diehl, H. S., and Sutherland, K. H.: Systolic Blood Pressure of Young Men, Arch. Int. Med. **36**:151 (Aug.) 1925.

23. (*a*) Fisher, J. W.: Mortality Statistics, Milwaukee, The Northwestern Mutual Life Insurance Company, 1935. (*b*) Report of the Joint Committee on Mortality of the Association of Life Insurance Medical Directors and the Actuarial Society of America, New York, 1925.

24. We have not discarded any of our extremely low blood pressure readings, for two reasons. First, in our sample less than 1 per cent of the readings for men and 1.8 per cent of those for women were below 90—an incidence which would not materially change our final results. Second, the dividing line between low and normal pressure has decreased steadily since the invention of the sphygmomanometer. Norris,[17b] in 1916, gave 115 mm., and Granger [17d] and others, fifteen years later, used 90 mm., as the lowest normal systolic blood pressure.

seen in the total group became proportionately less conspicuous as the upper levels were discarded. At the level of 140 mm. a significant difference from the previous distribution was noted: The mean level of blood pressure was nearly constant at all ages (chart 1). The mean blood pressure does not rise with age. The same type of serial elimination was carried out for the diastolic pressures, and the same tendency was apparent at the 90 mm. level.

The exclusion of pressures over 140 systolic and 90 diastolic does not alter the conclusions of the analysis. The results in our series would have been substantially the same had the level of delimitation been placed at 150 systolic and 95 diastolic. In addition, the modal pressure of the total group with its standard deviation—a more accurate measure of normal range—extends from 106 to 126 mm. of systolic pressure, which is essentially what is found in the delimited group. The technic of delimitation is only one of several methods which we have used to establish a normal range. The modal pressure of the total group, the continuous records of blood pressure and the study of mortality at different levels of pressure are all essential in establishing a true normal range.

Composition of Delimited Group (9,473 Persons).—When the persons with gross hypertension (temporarily and arbitrarily set at 140 systolic and 90 diastolic and over) were excluded from the total group, 13.3 per cent of the men and 11.5 per cent of the women were discarded because of obviously high pressure, leaving 6,458 men and 3,015 women within the delimited range. A statistical study of such a group should come closer to determination of normal levels than a study of the original sample.

Age Distribution.—The mean age of the men was 38.3 ± 0.14. The women were generally two years younger, with a mean age of 36.1 ± 0.19. The median age for the men was 37.1, showing a skewness of 0.32 to the left. From this it is apparent that the older age groups caused a slightly greater distortion of the mean than did the younger age groups; hence we did not have a perfect chance distribution. The median age for the women was 35.1, with a skewness of 0.29. This shows about the same distortion of the mean as the value for men, both figures showing a slightly significant distortion, in which case the modal age, 34.7 for men and 33.1 for women better shows the most intense concentration of the person in this sample of the population. As the standard deviation of the mean for men was 11.09 and that for women was slightly less, being 10.26, the distribution of the subjects around the points of central tendency shows that two-thirds were between the ages of 27 and 49 years and 95 per cent were between the ages of 17 and 61.

Distribution of Systolic Blood Pressures.—When the extreme end of an array is discarded, as we have done by eliminating cases of gross hypertension, the mean or arithmetic average will automatically decrease, but in a good distribution the mode should not change. This holds true for our sample. While the mean pressure for the total group of men was 121 ± 0.20 mm., the mean for the limited group was 116.3 ± 0.14 mm.; the mode for the total group of men was 115.9 mm., and the mode for the limited group was nearly identical, 115.1 mm. A standard deviation (two thirds of the distribution around the mean) of 10.92 mm. in the limited group shows that the systolic blood pressures of men (table 2) seemed to center around 105 to 127 mm. (116 ± 10.91 mm.).

This follows nicely in the array for women (table 3). The distortion of the mean in the total group caused a corresponding slight distortion of the mode, and while the expected fall of the mean occurs—from 117 to 111.6 mm.—the mode shows only a fall from 113.9 mm., in the total group, to 111.6 mm., in the delimited group. Because the mean and the median approximate each other in the limited group, 111.6 mm. seems more reliable. With a standard deviation of 12.3 mm., it seems safe to conclude that the systolic blood pressures of this group of women, regardless of age, ranged from 100 to 125 mm.[25]

To state this in simpler and more exact terms, the percentage groupings of the distribution were as follows:

6,458 Men	3,015 Women
86% between 90 and 130 mm. systolic	89% between 90 and 130 mm. systolic
54% between 100 and 120 mm. systolic	56% between 100 and 120 mm. systolic
6% below 100 mm. systolic	18% below 100 mm. systolic
25% below 110 mm. systolic	44% below 110 mm. systolic

When one considers that 44 per cent of the women and 25 per cent of the men had a systolic blood pressure below 110 mm., whereas the percentage with a pressure over 140 mm. was about the same for men and women, it is seen that women are more likely to have extremely low pressures than are men. However, this must be qualified by noting that women with low blood pressures were in the younger age groups.

A study of the correlation of systolic blood pressure with age is more informative. In the delimited group of men (chart 2) the distribution of low blood pressures did not show a significant change at any

25. If all of the men were lined up in the serial order of ascending systolic blood pressure the middle man of the group would have a pressure of 115.9 mm. The skewness of the distribution for men was 0.11, the distribution for women had no skewness and the median was the same as the mean, 111.6 mm. The greater coefficient of variation for women than for men is due to a fundamental difference between the distributions for men and for women when age is taken into consideration.

TABLE 2.—*Relation of Age to Blood Pressure in 6,485 Men in the Delimited Group (Pressures Over 140/90 mm. Excluded)*

	Age Groups																Percentage of Total Number
	Under 15	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80 and Over	All Ages	
Systolic pressure, mm.																	
Under 90	3	..	3	4	7	4	7	5	6	1	2	..	..	..	..	42	0.6
90- 99	8	5	22	52	56	63	60	40	20	18	7	3	2	..	..	356	5.5
100-109	2	10	83	192	230	233	174	155	75	50	23	8	2	2	..	1,239	19.1
110-119	3	33	167	351	411	392	300	247	143	77	39	16	10	1	1	2,191	34.0
120-129	1	35	159	295	297	289	259	194	109	85	53	22	6	1	1	1,806	27.9
130-139	..	9	69	146	124	111	129	91	65	51	30	15	7	2	2	851	13.1
Total	17	92	503	1,040	1,125	1,092	929	732	418	282	154	64	27	6	4	6,485	100.0
Percentage of total	0.3	1.4	7.7	16.0	17.4	16.9	14.3	11.3	6.5	4.4	2.4	1.0	0.4	0.1	0.1	100.0	
Mean	98.7	117.4	117.3	116.8	115.7	115.4	116.3	115.8	116.6	117.6	118.6	119.9	119.9	119.2	125.0	116.3	
Standard deviation	12.08	10.15	10.58	10.72	10.58	10.49	11.18	10.95	11.18	11.66	11.62	11.09	11.40	....	....	10.92	
Standard error	2.93	1.06	0.47	0.33	0.32	0.32	0.55	0.40	0.55	0.69	0.94	1.39	2.19	....	....	0.14	
Mode	92.5	122.5	119.7	115.9	113.3	113.0	116.9	111.9	116.0	121.5	124.9	124.7	120.2	....	....	115.1	
Percentage under 100	64.7	5.4	5.0	5.4	5.6	6.2	7.2	6.2	6.2	6.7	5.8	4.7	7.4	....	....	6.7	
Percentage under 110	76.4	16.3	21.5	23.9	26.1	27.5	25.9	27.4	24.2	24.4	20.7	17.2	14.8	33.3	....	25.3	
Percentage under 120	94.1	52.2	54.7	57.7	62.7	63.4	58.2	61.1	58.4	51.7	46.0	42.2	51.8	50.0	25.0	59.2	
Percentage under 130	100.0	90.3	86.4	86.1	89.1	89.8	86.1	87.7	84.4	81.9	80.4	76.6	74.0	66.7	50.0	86.9	
Diastolic pressure, mm.																	
Under 60	11	11	41	71	61	45	32	30	18	9	9	5	2	2	..	347	5.4
60-69	3	43	184	337	335	297	231	190	101	66	48	24	6	2	..	1,867	28.8
70-79	3	30	203	459	546	512	429	325	191	139	66	26	16	1	4	2,950	45.6
80-89	..	8	75	173	183	238	237	187	108	68	31	9	3	1	..	1,321	20.4
Total	17	92	503	1,040	1,125	1,082	929	732	418	282	154	64	27	6	4	6,485	100.0
Percentage of total	0.3	1.4	7.7	16.0	17.4	16.9	14.3	11.3	6.5	4.4	2.4	1.0	0.4	0.1	0.1	100.0	
Mean	56.0	68.0	70.2	71.1	71.6	72.6	73.4	73.3	73.4	73.3	71.9	69.9	71.2	66.7	72.5	72.1	
Standard deviation	9.80	7.68	8.37	7.87	7.62	7.81	7.75	8.06	7.81	7.62	8.06	8.12	6.48	....	....	7.97	
Standard error	2.38	0.80	0.37	0.24	0.23	0.24	0.38	0.30	0.38	0.45	0.65	1.02	1.25	....	....	0.10	
Mode	50.6	67.7	72.3	72.9	73.1	72.9	73.4	73.0	72.5	73.0	72.2	72.6	73.9	....	....	73.0	
Percentage under 60	64.7	12.0	8.2	6.8	5.5	4.2	3.5	4.2	4.3	3.2	5.8	7.7	7.4	33.3	....	5.4	
Percentage under 70	82.3	58.8	44.8	39.2	35.3	31.4	28.3	30.2	28.5	26.6	36.9	45.2	29.6	66.7	....	34.2	
Percentage under 80	100.0	91.4	85.2	83.3	83.8	78.3	74.5	74.6	74.2	75.9	79.7	85.7	88.9	83.4	100.0	79.8	

TABLE 3.—*Relation of Age to Blood Pressure in 3,015 Women in the Delimited Group (Pressures Over 140/90 mm. Excluded)*

	Age Groups															All Ages	Percentage of Total Number
	Under 15	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80 and Over		
Systolic pressure, mm.																	
Under 90	..	3	7	15	16	6	7	1	..	..	1	..	..	..	..	56	1.9
90- 99	4	14	62	102	97	82	66	28	14	7	3	1	1	..	..	481	16.0
100-109	2	27	100	141	156	148	92	58	36	15	4	3	1	..	..	783	26.0
110-119	4	27	85	161	186	157	123	72	44	26	7	3	..	..	..	895	29.6
120-129	2	6	36	73	101	97	83	60	40	22	12	3	..	..	..	535	17.7
130-139	..	2	11	30	30	34	53	48	23	16	11	5	1	1	..	265	8.8
Total	12	79	301	522	586	524	424	267	157	86	38	15	3	1	..	3,015	100.0
Percentage of total	0.4	2.6	10.0	17.3	19.4	17.4	14.1	8.9	5.2	2.9	1.3	0.5	0.1	0.03	..	100.0	
Mean	106.7	107.2	108.3	109.4	110.4	111.4	113.1	115.9	116.0	117.7	119.9	119.8	109.2	132.5	..	111.6	
Standard deviation	10.95	10.25	11.05	11.96	11.70	11.62	12.88	12.57	11.75	12.12	13.56	13.53	....	....	....	12.27	
Standard error	3.16	1.15	0.64	0.52	0.48	0.51	0.63	0.77	0.94	1.31	2.20	3.50	....	....	....	0.22	
Mode	101.6	110.2	106.8	111.5	112.5	111.1	112.5	112.9	113.9	115.9	126.1	....	....	....	....	111.6	
Percentage under 100	33.3	21.7	22.9	22.4	19.3	16.8	17.2	10.9	8.9	8.1	10.5	6.7	33.3	....	....	17.8	
Percentage under 110	50.0	55.9	56.3	49.6	45.9	45.0	38.9	32.6	31.8	25.6	21.0	26.6	66.6	....	....	43.8	
Percentage under 120	83.3	90.1	84.5	80.5	77.7	75.0	67.9	59.6	59.8	55.8	39.5	46.7	66.6	....	....	73.5	
Percentage under 130	100.0	97.7	96.5	94.4	94.9	93.5	87.4	82.1	85.3	81.4	71.1	66.7	66.6	....	....	91.2	
Diastolic pressure, mm.																	
Under 60	5	25	76	114	106	65	57	25	11	10	4	2	..	..	..	500	16.6
60-69	4	33	123	199	222	195	131	80	44	26	10	3	2	1	..	1,073	35.6
70-79	1	18	88	163	179	203	159	108	69	34	12	7	1	..	..	1,042	34.6
80-89	2	3	14	46	79	61	77	54	33	16	12	3	..	..	..	400	13.3
Total	12	79	301	522	586	524	424	267	157	86	38	15	3	1	..	3,015	100.0
Percentage of total	0.4	2.6	10.0	17.3	19.4	17.4	14.1	8.9	5.2	2.9	1.3	0.5	0.1	0.03	..	100.0	
Mean	64.2	63.5	65.3	66.7	68.0	69.0	70.1	71.2	71.7	70.9	72.9	71.2	67.5	67.5	..	68.5	
Standard deviation	9.43	8.17	7.81	8.71	9.17	8.09	8.95	8.57	8.24	8.71	9.83	8.06	....	....	..	8.85	
Standard error	2.73	0.92	0.45	0.38	0.38	0.35	0.43	0.52	0.66	0.94	1.60	2.08	....	....	..	0.16	
Mode	55.5	62.3	62.9	63.7	67.1	72.3	72.8	73.0	73.5	73.3	76.8	72.5	....	....	..	70.3	
Percentage under 60	41.6	31.7	25.3	21.8	18.1	12.4	13.4	9.4	7.0	11.6	10.6	13.3	....	....	..	16.6	
Percentage under 70	74.9	73.5	66.2	60.0	56.1	49.6	44.2	39.3	35.1	41.9	36.9	33.3	66.6	100.0	..	52.2	
Percentage under 80	83.2	96.3	95.4	91.3	86.6	88.3	81.7	79.7	79.1	81.4	68.5	80.0	100.0	100.0	..	86.8	

age.[26] As many 55 year old as 20 year old men had blood pressures under 100 mm. The same held true for pressures under 110 mm. The number with pressures over 120 mm. showed a slight increase with age. Up to the age of 60, one half or more of the men of all ages in the limited group had a systolic blood pressure lower than 120 mm. There was an increase in incidence of pressures over 130 mm. with increase in age. Apparently (table 2), most men who have low pressures (under 110 mm.) do not show any rise in systolic pressure throughout their lives, and about a tenth of the men with pressures under 120 mm. may show a slight rise in pressure after the fiftieth year. Finally the systolic pressures of about half the men of any age in this limited group did not rise above 120 mm., and that of about three-quarters never rose above 130 mm.

Because most of the variation in pressures occurs at levels over 120 mm., our data so far seem to indicate that the hypertensive men are

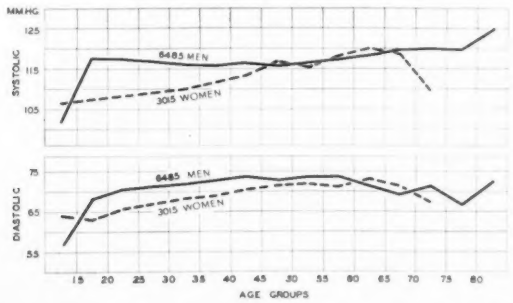

Chart 2.—Effect of age on blood pressure. After the obviously hypertensive persons are excluded, the limited group of men, with pressures under 140 systolic and 90 diastolic, shows little tendency toward a rise in blood pressure with age. The blood pressure of women is lower than that of men in the younger age groups.

those who have had systolic pressures above 120 mm. at an early age. In other words, men with moderately high systolic pressures (120 to 140 mm.) at any age, but especially in the younger group, are probably the ones who will have hypertension years later.[27]

The age distribution of systolic pressures for women shows one striking difference from that for men. While women over 40 years of age have about the same blood pressure as do men, younger women have substantially lower pressures. The mean systolic pressure of women under 40 years of age was 110.4 mm.; that of men was 117 mm.

26. The coefficient of correlation of age with systolic pressure for men in the limited group was 0.02 ± 0.01; for women it was 0.22 ± 0.01.

27. A study of our ten year continuous records will confirm this.

After the age of 40 the mean pressure was about 118 mm. for both men and women. The change in women is not sudden but is a steady climb in mean pressure, starting just after the age of 20 and continuing into old age. To emphasize these low pressures in young women, we note that about 50 per cent had pressures under 110 mm. and more than 20 per cent had pressures under 100 mm. (table 4).

While there was an incidence of 2 per cent of readings under 90 mm. for the young women, only a few low readings were found for women after the age of 40. In men the incidence of readings under 90 mm. was greater in the old than in the young. It is interesting to note, however, that there were twice as many women as men whose systolic pressure was under 100 mm. and as many women whose systolic pressure was under 90 mm., even in the older age groups. Almost 80 per cent of the young women showed systolic pressures under 120 mm., and the systolic pressures of more than 60 per cent of the older women were

TABLE 4.—*Distribution of Blood Pressure in Men and Women*

Blood Pressure, Mm.	Men		Women	
	Under 40 Years of Age, %	40 Years of Age and Over, %	Under 40 Years of Age, %	40 Years of Age and Over, %
Under 90	0.5	0.8	2.3	0.9
Under 100	5.9	6.5	20.2	13.0
Under 110	25.2	25.2	48.6	34.1
Between 110 and 120	35.1	31.9	30.6	27.8
Over 120	39.7	42.9	20.9	38.1
Over 130	11.9	15.0	5.3	15.9
Number of cases	3,869	2,616	2,024	991

under 120 mm. In men the difference between young and old was less marked. We have seen that the percentage of women with systolic pressures over 110, 120 and 130 mm. increases with age.

From this distribution it is apparent that most women have low blood pressures up to the age of 40 and that the pressures will be slightly higher after 40, but are lower than at the corresponding ages in men. The systolic pressure of about one half of the population never greatly exceeds 120 mm. A rise in pressure in women is deceptive unless it is realized that women start with pressures far below those of the men. The modal pressure of women is lower than that of men even in the older age groups. Almost half the younger women have pressures under 110 mm. Younger women generally have systolic pressures up to 15 mm. lower than those of young men, and older women have pressures equal to or less than those of older men. It must be remembered that we are not concerned with hypertensive women when we say this.

Distribution of Diastolic Blood Pressures.—The mean diastolic pressure for men was 72.1 mm., with a modal pressure of 73 mm. The

women had a mean pressure of 68.5 mm. and a modal pressure of 70.3 mm. The standard deviation for men was 7.9 mm. and that for women was 8.8 mm. Thus, the men usually had diastolic pressures between 64 and 80 mm., while for women the values were slightly lower, between 60 and 77 mm. (tables 2 and 3).

When this distribution is analyzed from the standpoint of specific age groups, the very low pressures in men are seen to occur chiefly in youths under 20 years of age; hence the mean shows a slight rise which after the age of 20 is not significant. We cannot, therefore, find a normal rise of diastolic pressure in normal persons.[28] A further corroboration of this is seen in the more pertinent fact that the modal pressure hovers around 72 to 74 mm. at all ages. However, the number of low diastolic pressures (under 70 mm.) decreases up to the age of 55 years, but after the age of 55 the number under 70 mm. returns to its earlier incidence. We have not adequately accounted for this variation. The percentage of diastolic pressures between 70 and 80 mm. remains constant throughout life. The percentage over 80 mm. increases in late middle age. Apparently this is the pressure which favors hypertension.

The diastolic blood pressure of women, like the systolic, varied slightly with age. The levels for older women were about the same as those for men, but the younger women (up to 30 years of age) usually had diastolic pressures at the lower 60 mm. level. As in the case of systolic pressure, the diastolic pressure of older women was not, on the whole, greater than that of men of corresponding age, but that of the younger women started at a much lower value.

It seems from the foregoing data that the diastolic pressure should normally be below 80 mm. It is hard to imagine why 90 mm. was ever chosen as the upper limit of normal. Even in the total group, with hypertensive persons included, we were able to establish the statistical fact that the greater number of persons had pressures below 80 mm. Because the diastolic fluctuation was less marked than the systolic and because the measurements with a central tendency were all in the low 70 mm. class, it seems from a purely statistical analysis that normal diastolic pressure should be 80 mm. or below. Alvarez,[17e] Sallar.[29]

This study of a delimited group of persons bears out our conclusions in the study of the modes of the total groups; that is, a great number of persons do not show a rise in blood pressure,[30] for in our delimited group at least half the older persons had systolic blood pressures below 120

28. The coefficient of correlation of age with diastolic pressure for men was 0.09 ± 0.01; for women it was 0.22 ± 0.1.

29. Saller, K.: Blood Pressure Changes Due to Age, Ztschr. f. d. ges. exper. Med. **58**:683, 1927.

30. MacWilliam, J. A.: Blood Pressure in Man Under Normal and Pathologic Conditions, Physiol. Rev. **5**:303, 1925.

mm. It is apparent that most men in this group had pressures around the 116 ± 10 mm. level at any age. Older women had pressures similar to those of men, but younger women had pressures much lower than men. The pressures which were most frequent for women were around 112 ± 10 mm. Furthermore, it seems from this study that hypertension occurs in persons who earlier in life have shown systolic pressures above 120 mm.

The diastolic levels appear to be in the low 70 mm. class most frequently for both men and women, although for young women they generally are lower. At any rate pressures between 60 and 80 mm. comprise the majority for both men and women. Pressures of 80 mm. and over should, in the light of this study, be classified as indicating hypertension.

Summary.—Many recent authorities agree that the upper level of normal blood pressure lies around 140 systolic and 90 diastolic. We have discarded all subjects with pressures above this level, a delimited group remaining in which the normal blood pressure of both men and women probably lies under 127 mm. systolic and 80 mm. diastolic. We have further demonstrated that the majority of persons do not show a rise of blood pressure with age. As many old men as young men have low blood pressures. We have still not explained the fact that the 10 per cent of the population which shows a rise in pressure had at an earlier age pressures which were apparently normal. It would be interesting to find out what those blood pressure levels were. Our study of static pressures shows that the major shift in incidence with increasing age falls within the groups showing pressures of over 120 systolic and 80 diastolic.

This is as far as any static study of pressure can take us. Although a static study shows clearly the major trends of blood pressure and the approximate levels at different ages, it does not take into account the daily and yearly variations in blood pressure. This continuously changing physiologic process can be measured only through a study of continuous records. The life history of blood pressure as a dynamic process is the topic of the next section.

CONTINUOUS BLOOD PRESSURE STUDIES

Ever since blood pressure became important as a diagnostic aid, workers in the field have bemoaned the fact that their material did not include studies of continuous blood pressure records over long periods. In a rather extensive review of the literature we have found only one or two studies that approach the problem from the standpoint of yearly blood pressure levels for presumably normal persons over a period of years. For our study of the continuous blood pressure of 500 apparently well men, each record contained the abstract of an annual physical

examination over a period of about ten years.[31] These records were taken under the same standardized conditions as were those of the previous group of 10,883 persons. The study endeavored to embrace all adult age groups and all levels of blood pressure.

1. The first characteristic that strikes one in even a casual perusal of yearly continuous records is the marked variation that every person's blood pressure shows. This yearly variation merely reflects the daily physiologic rhythm of blood pressure. The pattern of this variation is much like that of temperature. It is lowest in the early morning, during sleep and highest in the late afternoon. Other factors, such as emotion and exercise, superimpose additional flux on the diurnal flow of pressure.

TABLE 5.—*Average Range of Differences Between Highest and Lowest Readings*

Number of Men	Systolic Pressure Level Always Over	Difference, Mm.
5	140 mm.	36
9	130 mm.	24
23	120 mm.	23
53	110 mm.	18
58	100 mm.	19

TABLE 6.—*Yearly Variation in Blood Pressure*

Systolic Pressure, Mm.	Number of Men	Average Mean Yearly Variation, Mm.
Never under 140	5	16.0
Never under 130	16	12.7
Never under 120	28	9.0
Never under 110	53	7.6
Never under 100	54	6.9
Under 100 in at least one reading	49	8.0

The average range of differences between the highest and lowest readings over a ten year span varies proportionately with the level of systolic pressure (table 5). At pressures over 140 mm. there is a difference of 36 mm. between the lowest and the highest reading, as compared with a difference of 19 mm. at a level of 100 mm.

2. Second, it was observed that blood pressures which were consistently low did not vary as much from year to year as those that were consistently high. From table 6 one sees that the higher pressures were definitely more erratic from year to year than were the lower pressures.

3. More illustrative than the simple average variation is the comparative percentage of each of the various groups which registered high

31. A complete statistical analysis of these continuous records will appear in a subsequent publication.

yearly ranges. Notice (table 7) that the persons who consistently showed high pressure over a span of years usually showed greater variation than did persons who consistently showed low pressure (chart 3). Comparison of another random sample of 15 men who *always* registered pressures over 120 mm. with 15 men who *never* registered pressures over 120 mm. showed an excess of 14 mm. in total range and of 4 mm. in mean range in the former group (chart 4). Further, the group with systolic pressures above 120 mm. showed a definite tendency to increased pressure with age while the group with systolic pressures below 120 mm. kept a constant level.

4. The fact that as pressures increase they tend to show wider variation suggests that the genesis of hypertension will show itself in transient elevation of pressure. A person usually does not become hypertensive suddenly, nor does the blood pressure rise steadily each year to higher levels. There is usually an ever increasing number of temporary excursions into higher levels. The effect of these temporary

TABLE 7.—*Degrees of Variation in Blood Pressure*

Systolic Pressure, Mm.	Percentage of Group Showing a Total Variation of			
	More Than 20 Mm.	More Than 25 Mm.	More Than 30 Mm.	More Than 40 Mm.
Always over 140	100	80	80	20
Always over 130	67	56	33	11
Always over 120	57	48	26	9
Always under 120	33	27	13	0

excursions is cumulative, the pressure continuing at a high level with only momentary lapses into low pressures. "The highest readings must not be disregarded."[32]

In observing a list of persons whose records are available for ten or more years, it was noticed that if the systolic pressure during the first years even once reaches a level above 130 mm. it is almost certain that that pressure will be exceeded before the tenth year is passed. For example, in the case of S. R. B., a man aged 43 whose pressure in 1928 was 134 mm., the systolic blood pressure was lower for the next two years; in 1931, however, it was 136 mm., and in 1933 it was 140 mm. It varied from 130 to 140 mm. until 1938, when it was 156 mm. An even more striking example is the case of E. L. M., a woman who at 53, in 1927, had a systolic pressure of 140 mm. In 1928 the systolic pressure was 122 mm. It varied around 130 to 140 mm. for the next four years, but in 1933 it rose to 146 mm. Some physicians would consider a pressure of 146 mm. as "normal," but the next three annual readings

32. Bolt, W.: Hypertension as an Underwriting Problem, Proc. A. Life Insur. M. Dir. America **21**:183, 1934.

ranged from 154 mm. to 220 mm., in 1938, at which time she had a stroke. E. L. M.'s systolic pressure of 122 mm. in 1928 was not normal (table 8).

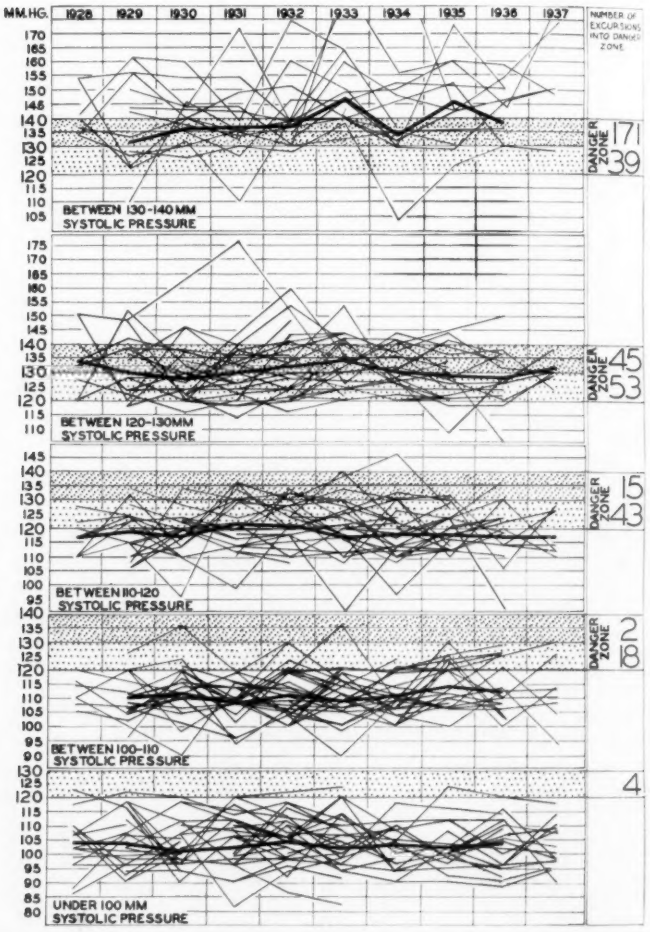

Chart 3.—Study of ten year continuous records. The five types of pressure records indicated in the graph were selected. Note that the lower pressures tend to maintain their levels and show smaller and less erratic variations. As the pressures increase the excursions into the danger zone become more frequent.

These observations are at complete variance with those of investigators who brush aside an occasional high reading. To quote one example, Stieglitz [33] stated: "Minor fluctuations of 15 to 20 mm. of pressure occurring under conditions of psychic strain are normally physiologic." We find that in most instances a "minor fluctuation" is the forerunner of hypertension. No data are available in the literature, so far as we can find, to support the opinion that minor fluctuations are normal. The only work that deals with the subject supports our results.[34]

As it becomes increasingly evident that the blood pressures which show intermittent excursions to high levels are those that lead to hypertension in later years, it would be interesting to find at which levels the blood pressure is most likely to make these transient excursions. In

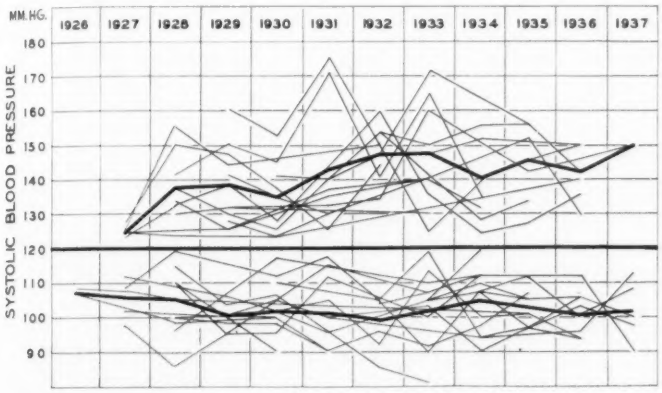

Chart 4.—Comparison of pressures always above 120 mm. systolic with those always below 120 mm. over a ten year span. This graph shows the tendency of systolic pressures which always remain under 120 mm. of mercury to maintain a steady level, with smaller and less erratic variations. The pressures which always register above 120 mm. tend to have greater and more erratic variations, with a tendency to rise with age.

order to study this problem, we divided a part of our continuous records into five groups, according to the frequency with which the lower read-

33. Stieglitz, E. J.: Emotional Hypertension, Am. J. M. Sc. **179**:775, 1930; footnote 13.

34. (*a*) Diehl, H. S., and Hesdorffer, M. B.: Changes in Blood Pressure of Young Men over a Seven Year Period, Arch. Int. Med. **52**:948 (Dec.) 1933. (*b*) MacKenzie, L. F.: The Significance of Hypertension, Proc. A. Life Insur. M. Dir. America **24**:157, 1937. (*c*) Palmer, R. S.: The Efficacy of Medical Treatment in Essential Hypertension, New England J. Med. **215**:569, 1936. Bolt.[32]

TABLE 8.—*Ideal Blood Pressures and Blood Pressures Indicating Incipient Hypertension*

Age at First Examination	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935	1936	1937	1938
						Ideal Blood Pressures							
32	112/84	114/70	100/68	100/70	98/70	102/78	98/70	92/68	100/74	104/ 74	108/ 68	92/ 68	.....
47	.....	100/66	100/64	106/68	100/70	102/72	104/72	90/58	98/66	106/ 70	100/ 60	106/ 68	84/56
57	104/68	102/68	106/66	108/68	100/70	100/72	110/74	118/68	94/77	.....	104/ 70	98/ 68	.....
64	.....	.....	102/74	110/66	102/70	102/58	118/70	.....	108/64	110/ 66	104/ 70	.....	108/72
55	.....	128/62	.....	124/72	110/68	98/70	122/68	120/60	122/64	112/ 60	120/ 72	110/ 78	.....
						Incipient Hypertension							
43	.....	134/94	126/90	.....	.....	136/88	130/86	140/98	130/92	140/100	132/104	142/102	156/96
66	.....	.....	110/74	146/86	136/72	132/70	146/82	132/74	142/76	114/ 78	144/ 86	136/ 80	.....
42	.....	.....	.....	136/90	120/70	132/76	122/80	134/84	160/78	148/ 80	142/ 80	.....	140/82
29	.....	132/80	.....	.....	132/92	140/84	136/80	130/78	126/78	140/ 90	122/ 82	136/ 86	144/88
38	.....	.....	.....	140/78	122/70	138/70	.....	134/70	154/78	126/ 75	120/ 72	142/ 72	.....

ings were obtained (chart 3). We then designated the levels of from 120 to 130 and 130 to 140 mm. systolic as danger zones of potential and actual hypertension. Persons whose systolic blood pressure periodically dips under 100 mm. only rarely enter the danger zone. As the level of pressure increases the excursions into the danger zones increase.

It seems evident that systolic pressures which regularly are above 120 mm. are bound to show transient elevation into the danger zone of 130 to 140 mm. The physiologic effect of these frequent daily periodic excursions into hypertensive levels may be the early groundwork of incipient hypertension. Because blood pressures are not static, a man whose systolic pressure does not dip below 120 mm. on successive readings must be potentially hypertensive. This is obvious when one takes into consideration his usual 15 mm. of diurnal rhythmic flux of pressure. Systolic pressures above 120 mm. are in the zone of hypertension, and transient elevations into the danger zone are an indication of incipient hypertension. A systolic blood pressure above 120 mm. cannot under these conditions be correctly considered "normal." To be sure one may not be able, with the present limited knowledge, to find objective evidence of pathologic change, but such a pressure does indicate the probable genesis of long, drawn-out disease.

5. Another, and probably the most important, finding is apparent among persons with low blood pressure, i. e., the tendency of systolic pressures below 120 mm. to maintain an even course throughout life. Low blood pressures rarely change their level in the direction of a steady rise. Of over 200 continuous low blood pressure records only 2 indicated an increase with age. From these lines of evidence it seems wholly justifiable to conclude that persons with low pressures continue at these levels throughout their lives, while those with moderately high pressures tend to have much higher pressures, usually after the age of 40 (chart 3).

Summary.—It is seen how the study of the life history of vascular tension gives a new impression of blood pressure. It introduces the concept of blood pressure as a dynamic physiologic force, and through the aid of this concept one comes to a comprehension of the growth, the maturity and possibly the senescene of that force. The blood pressure undergoes continuous change throughout the twenty-four hours of each day. Statistical studies on isolated blood pressure readings are forced to treat these readings as static phenomena. It is undoubtedly important to be aware of the general level of blood pressure in large groups of persons, but it is far more important to know the surging and resurging flow of the ever changing compensations in pressure in persons who do and in persons who do not have hypertension. We have shown that there is a difference in the daily changing tensions of the vascular system in the healthy and in the prehypertensive person. We have shown that pressures under 120 mm. are less variable and less

erratic than are pressures continuously over 120 mm. and that transient excursions into the danger zones of hypertension are rare in persons with low pressures. Further, pressures under 120 mm. tend to maintain a constant level, while those over 120 mm. rise with increasing age. We conclude from this study of continuous records that the range of normal systolic blood pressure must not extend above an upper limit of 120 mm.

MORTALITY RATE AT DIFFERENT BLOOD PRESSURE LEVELS

The next problem that logically follows a study of the life history of blood pressure is the mortality of persons with different levels of tension. This death record provides a natural confirmation of the long term trends of different blood pressure levels observed during life. It is essential that the physician know where he stands in the control of morbid processes; he cannot pronounce persons "normal," "healthy," or "free from disease," unless he is constantly aware of the factors which shorten life and of those which contribute to long life. The physician's most accurate check on the potential longevity of his patient is the patient's deviations from physiologic norms. Mortality statistics place the patient in the perspective of potentiality. When the level of a clinical measurement falls in a category with an extremely high mortality rate, obviously that level is abnormal and the patient is not "healthy," no matter how well he feels. For example, when we learn that excessive weight is associated with a terrifically high mortality, almost pound for pound, even the moderately overweight person must be considered abnormal. The same is true of the pulse rate, for which the norm, for generations fixed at 72 ± 10 beats per minute, is found in the light of mortality studies to be associated with a higher death rate than is a pulse rate of 50 to 65. To the physician this should mean (chart 5) that the norm is too high.[35]

With blood pressure, as with weight and pulse, one should look on the mortality rate as a check on the levels one accepts as normal. From our statistical study and our continuous records we decided that 120 systolic and 80 diastolic are "upper limits." This cannot be true unless it checks with the best mortality rate. In chart 5 we find complete accord with our conclusions. With a rise in blood pressure there is an abrupt rise in the death rate. This rise begins with the very low pressures. By no stretch of the imagination can pressures of 130 to 140 mm. be considered normal. Diastolic pressures over 80 mm. are associated with an increase in the death rate that is not compatible with the word "norm."

35. Sydenstricker, E.: Physical Impairment and Occupational Class, Pub. Health Rep. **45**:34, 1930. Morgan, P. W.: The Status of Persons with Sinus Bradycardia, J. Kansas M. Soc. **37**:455, 1936.

Most medicoactuarial experience with blood pressure levels speaks in favor of low pressure. The Northwestern Mutual Life Insurance Company [23a] found a mortality ratio of 35 per cent for pressures under 100 mm. as compared with 94 per cent for pressures averaging 142 mm. and 114 per cent for pressures averaging 153 mm. (table 9). There was a steady increase in mortality with increase in pressure. Fisher [36] (table 10) cited a mortality study which corroborated this step like rise in mortality with increase in pressure.[37]

The records of the Prudential Life Insurance Company [171] (table 11) show that low mortality rates fall in a classification of an underaverage diastolic blood pressure, though the authors of the report, MacKenzie

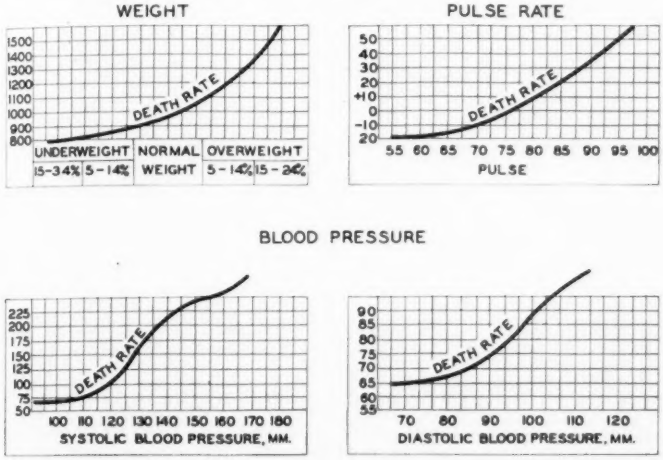

Chart 5.—Mortality trends for various physiologic measurements, showing in all cases that the higher readings are accompanied by a rapidly mounting death rate. The low readings are the most desirable; in all measurements they are associated with the lowest mortality. The weight curve was modified from Dublin and Lotka,[1a] tuberculosis being excluded. The pulse curve was adapted compositely from P. W. Morgan (Morgan, P. W.: The Status of Persons with Sinus Bradycardia, J. Kansas M. Soc. **37**:455 [Nov.] 1936), Rogers and Hunter 5f and Dublin and Lotka.[1a] Blood pressure curves were derived compositely from statistical material cited in the section on mortality.

and Wells, did not agree with the preceding authors in regard to the favorable mortality rate of the very low systolic pressures. Living-

36. Fisher, J. W.: Report of Committee on Low Blood Pressure, Proc. A. Life Insur. M. Dir. America, 1917, p. 204.

37. Fisher, J. W.: Use of Sphygmomanometer, Proc. A. Life Insur. M. Dir. America, 1907-1912, p. 393.

ston [38] also found a slightly higher mortality with the very low systolic pressures, but even so it is 13 per cent lower than the average. Thus, as both systolic and diastolic pressures are similarly disposed as to mortality rates, one would expect that the combination of systolic and diastolic pressures would produce a similar disposition. Bolt [32] confirmed this in a study of "mean" blood pressure $\frac{(\text{systolic} + \text{diastolic})}{2}$ and stated [39]: "Our New York Life experience shows mortality directly proportional to the high readings. *There are too many physicians who underestimate the seriousness of a moderate elevation of pressure.*"

TABLE 9.—*Experience of Northwestern Mutual Life Insurance Company* *

Range of Arterial Tension	Ages at Entry	Ratio of Actual to Expected Mortality, %
Low blood pressure (100 mm. and under)	16-60	33
Average blood pressure of 142 mm.	40-60	90
Average blood pressure of 153 mm.	40-60	115

* Expected mortality, 80 per cent.

TABLE 10.—*Life Expectation of Persons with Hypertension (American Actuarial Society)*

	Percentage
Expected deaths according to American actuarial tables	100
Pressures of 105 mm. and under	47
Pressures of 106-100 mm.	65
Usual experience with accepted risks	86
10-14 mm. over average pressure for age	114
15-24 mm. over average pressure for age	181
25-34 mm. over average pressure for age	205
35-44 mm. over average pressure for age	246
45-49 mm. over average pressure for age	254
60 mm. and more over average pressure for age	450

Dublin and Lotka,[1a] Southby,[40] Fraser,[41] Muhlberg,[42] Brown [43] and Rogers and Hunter [5f] unanimously confirmed this conclusion.

The most extensive investigation of the relation of mortality to blood pressure was made by the Joint Committee on Mortality of the Associ-

38. Livingston, J. M.: Blood Pressure Normal and Abnormal, Canad. M. A. J. **30**:54, 1934.

39. Bolt, W., in discussion on MacKenzie.[34b]

40. Southby, R.: Clinical Observations on Blood Pressure with Special Reference to Variation of Blood Pressure Readings in the Two Arms, M. J. Australia **2**:569, 1935.

41. Fraser, R. A.: Life Insurance in the Service of America's Health, Proc. A. Life Insur. Pres. **28**:53, 1934.

42. Muhlberg, W.: Medical Resources and Mortality Trends, Proc. A. Life Insur. Pres. **27**:142, 1933.

43. Brown, in discussion on Rogers and Hunter.[5f]

44. Footnote deleted by author.

ation of Life Insurance Medical Directors and the Actuarial Society of America. The report of this committee was an analysis of the records of 707,000 policy holders, which were submitted by twenty-six leading insurance companies in the United States and Canada. The Joint Committee on Mortality [23b] concluded that the underaverage pressures were associated with a lower mortality than was the "average" pressure in every age group (table 12). Hay [9] aptly summed up these findings in his statement: "There is something dramatic and ominous in the steady diminution in the expectation of life accompanying a rise of blood pressure."

It seems that mortality studies are in complete accord in condemning the popular notion that low blood pressure is a disease and moderately

TABLE 11.—*Ratio of Actual to Expected Mortality Rate (American Men's Standard) for Standard Risks According to Diastolic Pressure (Prudential Life Insurance Company)*

Ages at Entry	Under 70 Mm.	70-79 Mm.	80-89 Mm.	90 Mm. and Over
15-29	60	77	100	104
30-39	47	67	64	81
40-49	47	55	63	60
50 and over	26	25	60	62
All ages	49	61	69	72

TABLE 12.—*Ratio of Actual to Expected Deaths for All Ages According to Pressure (Joint Committee on Mortality)*

	Underaverage 5 to 15%	Average	Overaverage 5 to 15%
Systolic	94%	100%	114%
Diastolic	94%	100%	116%

high pressures are "normal" and safe.[45] Part of the definition of a normal person is that he must live long, be relatively free from illness and not be prematurely killed off by degenerative diseases. Invariably this is the person with a low weight, a low pulse rate and a low blood pressure.[46] This triad of physiologic levels is the foundation stone on which longevity is built. Symonds,[46b] in his widely quoted work on

45. Garvin, J. D.: Hypotension: Report of Six Cases in One Family, J. A. M. A. **88**:1875 (June 11) 1927. Friedlander, A.: Clinical Types of Hypotension, ibid. **83**:167 (July 19) 1924. Roberts, D. M.: Hypotension or Low Arterial Pressure, Illinois M. J. **71**:448, 1937. Brower, A. B.: Hypotension, Ohio State M. J. **33**:152, 1937. Blackford, J. M.; Bowers, J. M., and Baker, J. W.: Follow-Up Study of Hypertension, J. A. M. A. **94**:328 (Feb. 1) 1930. Lewis, T.: Diseases of the Heart, ed. 2, New York, The Macmillan Company, 1937.

46. (*a*) Gregory, J. R.: Variations in Blood Pressure and Their Clinical Significance, East African M. J. **14**:3, 1937. (*b*) Symonds, B.: Blood Pressures of Healthy Men and Women, J. A. M. A. **80**:232 (Jan. 27) 1923.

blood pressure, stated: "It would seem that the average pressure runs counter to the best interests of health." The Joint Committee on Mortality [28b] expressed agreement: "The average blood pressure does not seem to be the pressure of lowest mortality." The normal person is the person with a blood pressure below average. In other words, the established "average," or normal, pressure of today is too high.

Summary.—These mortality records from a variety of insurance companies all agree that pressures over 140 systolic and 90 diastolic are definitely associated with a proportionately increased death rate. They all agree further that a higher mortality is to be expected among persons with pressures of 130 systolic and 80 diastolic than those in the pressures of 120 systolic and 80 diastolic. Many go further and show that a pressure of 110 systolic and 70 diastolic is associated with a lower mortality rate than one of 120 systolic and 80 diastolic. Some of the companies indicate that pressures below 110 systolic and 70 diastolic may have the best mortality rate. In general, the mortality of any random group of 1,000 persons with pressures over 120 systolic and 80 diastolic is higher than that of a similar group with pressures under these levels.

COMMENT

The status of knowledge concerning blood pressure is such that the wide divergence of authoritative opinion as to what constitutes "normal" has given rise to much confusion. The upper level of normal systolic pressure, according to contemporary literature, can extend from 120 to 160 mm.; the diastolic limits, anywhere from 90 to 110 mm. However, during the past decades the preponderance of opinion regarding normal levels has shifted toward lower limits. The confusion which invariably results from a shifting level has made itself felt in recent medical texts. Many authors do not commit themselves as to normal levels, and those who do take a stand give two levels, with a "no man's land" between. Moreover, the tendency to establish norms and then disregard them seems indicative of growing uncertainty of the norms which were established. It is, of course, dangerous for an author to commit himself to a fixed norm in the face of conflicting opinion, but in no field of modern medicine is there greater need for clarification than in that of blood pressure. We feel strongly that it is dangerous even unwittingly to evade the paramount issue of narrowing the extremely wide range that now exists for normal blood pressure.

We have attempted to explain in detail the reasons why such confusion exists. We have further pointed out that all past studies relied too exclusively on statistical data. Such studies have value, but in order to arrive at any physiologic norm it is necessary, in addition, that

an analysis of the life history of the measurement be made and then correlated with mortality data. The interplay of all of these factors must be taken into account before one can establish a physiologic norm.

We have shown that it is statistically as well as physiologically in error to group together for study normal and pathologic subjects in order to arrive at normal levels. Such a study will give the sum total of the data for both groups. Our study has taken full cognizance of the inherent danger of such a mixed group and accordingly has, at the outset, discarded the obviously hypertensive subjects, whose presence has led so easily to misinterpretations of "normal" in the past.

We have, however, submitted the data on our total group with several breakdowns of statistical treatment (table 1) for those who are especially interested or who wish to to make comparisons with other existing data.

The only valid and significant conclusions that we were able to draw from our total group related to diastolic blood pressure. Most previous studies of blood pressure have established 90 mm. as the upper limit of normal, some giving 95 and others 100 mm. and over. From a study of our total group, a statistical analysis alone, without inclusion of other data (which we look on as absolutely essential in arriving at norms), we place the upper limit of normal diastolic blood pressure at about 80 mm.

The first step in our statistical analysis was to eliminate the obviously hypertensive subjects. We decided to eliminate all readings above 140 mm. systolic or 90 mm. diastolic as definitely pathologic, since this was a level accepted by many recent writers. Slightly more than one tenth of our subjects were discarded as grossly hypertensive, but by no means did we eliminate all of the hypertensive persons. As was shown later, many were included. The statistical analysis was completed on this delimited section of the total: a smaller, select sample, more nearly normal than any total group.

Study of this delimited group shows that men usually have a blood pressure of 115 ± 10 mm. systolic and 72 ± 8 mm. diastolic; women show pressures of 112 ± 10 mm. systolic and 70 ± 8 mm. diastolic. These facts should indicate that the upper limits of blood pressure must be under 125 systolic and 80 diastolic. We further showed to be true what a few astute observers [47] have long believed, that normal blood pressure does not rise with age. We confirmed in this study of the delimited group the findings of some previous workers that young women have lower pressures than young men and showed that older women have substantially the same, or slightly lower, pressures than older men.

47. Stocks, P., and Karn, M. N.: Blood Pressure in Early Life, London, Cambridge University Press, 1924. MacWilliam.[30] Alvarez.[17e] Dingman.[17j] Hunter.[16] Huber.[17g]

These conclusions were drawn from analyses of static statistical tables, but blood pressure is so overwhelmingly a dynamic process that a study of the flux of pressure levels over a period of years was felt to yield far more important results. No study can be complete unless the life history of blood pressure is taken into account. Therefore, we analyzed a group of 500 records continuous over a period of five to ten years.

When we followed the course of blood pressure in its aberrations over a period of years, we noticed first the year to year variations. Much of this variation, it was decided, is due to the normal diurnal flux of pressure, which emulates temperature, pulse and the diurnal harmonics of metabolism. A second observation was that the lower pressures did not show as great a variation—usually it was less than 10 mm., while the higher pressures usually varied by 15 to 40 mm. Third, low pressures almost invariably tended to remain at the same general low level throughout all age groups, while the higher pressures showed definite signs of rising to even higher levels with advancing years. It was shown that blood pressure readings persistently below 120 mm. remained at the same level throughout a ten year period in any age group and had little variation, while systolic blood pressures persistently above 120 mm. showed a tendency to rise over a ten year span in all age groups and showed greater and more erratic variation. From these continuous records we concluded that normal systolic blood pressure should not exceed 120 mm.

It was further shown that once a person's pressure shows even intermittent rises into the danger zones of 120 to 130 and 130 to 140 mm. it frequently returns to that level. We suspected that these excursions into the danger zone tended to become more and more frequent and considered these pressures as indicating incipient hypertension.

Another important measure available for a check on the norms is a study of mortality data. The word "normal" is inconsistent with a high mortality rate. Whatever the method of selecting any physiologic norm, the level cannot be interpreted medically as "normal" unless it is consistent with the longest possible life.

What is the vascular tension that leads to the longest life span, and what are the levels that shorten life? This question is of the greatest interest in our study because it forms a background for our definition of "normal." There is overwhelming evidence from available actuarial material that shows increased mortality to be directly proportional to increased blood pressure. And what is of the greatest significance is that the increase commences at below average levels. In other words, men with blood pressures of 120 mm. and over will die sooner than men with blood pressures under 120 mm. It is thus seen that mortality data completely corroborate the low levels of blood pressure, i. e., under 120 systolic and 80 diastolic, which we have established as normal.

It can be seen from these new levels of blood pressure that there is now an entirely different picture of hypertension, which fits in far more coherently with the picture of hypertensive heart disease and its high death rate. The incidence of high blood pressure is much higher than is generally realized; about 40 per cent of the adult population is prehypertensive or hypertensive. Hypertension is a long term disease, not a short term degeneration beginning after the fortieth year; almost as many young persons as old persons have potential or actual high blood pressure, the only difference being in the severity of the condition. Hypertensive heart disease starts during youth, and its diagnostic sign is a persistent elevation of blood pressure into levels over 120 systolic and 80 diastolic; frequent intermittent excursions above these levels denote incipient hypertension.

We have stressed the flux, or movement, and variability of blood pressure. This seemed to indicate that when one looks for normal levels one must consider the task as one not merely of selecting a fixed point—120 or 130 mm.—but of picking a range of blood pressure readings within which normal surging movement of vascular tension takes place. One cannot expect to interpret the phenomenon of a fluctuating pressure head moving within viscous fluid down a branching system of elastic tubes on the basis of a single static number. The very nature of blood pressure is movement, and in the future blood pressure must be designated as a range of movement. Much of the older work has seriously handicapped the usefulness of the sphygmomanometer by giving physicians the impression that man's blood pressure should be fixed at a static level of 120 or 130 mm. Blood pressure must be interpreted as a range of systolic and a range of diastolic pressure. If one records a patient's blood pressure for the first time at 120 mm., he may be either hypertensive or normal. If over a period of years the 120 mm. reading is the lowest pressure, he is hypertensive; if it is the highest pressure, he is normal.

In the face of a value which is in constant variation, it is easy to see why some investigators have given up the hope of establishing norms for blood pressure. Dr. Clarence L. Andrews, in a talk before the American College of Physicians, stated that "there is no such thing as 'normal' pressure at any period of life; what is normal for one man may indicate disease for another." This is a dangerous axiom that is gaining ground in current medical thought. No abnormal physiologic level is normal for any given person. No person can carry higher than normal physiologic levels with impunity. Men die sooner if the pulse rate, the temperature, the weight and the blood pressure are only slightly elevated above the established "normal" levels. An occasional exception must not sidetrack one from the immutable laws that inevitably lead the overwhelming majority of persons with abnormal readings to an early death. After all, these physiologic levels have been fixed over millions

of years of evolutionary ascent. The range of blood pressure must be considered to be as immutable and as constant as the temperature and pulse rate. If by "normal" one means the probability of a long life, a low morbidity rate and efficient activity, it is almost obvious that there is a normal-healthy range of blood pressure and an abnormal, diseased range.

Who is the normal person? Surely he is one who is free from disease, discernible or latent—one who is subjectively well. The fact that he has no latent disease is learned through a consideration of simple clinical tests. However, these clinical tests in almost every category have described a range of "normal" far too wide and not consistent with the best mortality rates, and physicians have begun to whittle away at the extremes of these too wide ranges. Compare the standard weight tables of twenty-five years ago with those published today. Statisticians formerly allowed more weight than can now be conceded even to civilized man, and allowed an increment with an increase in age. It is generally accepted now that optimum weight remains constant after maturity is reached, at about the age of 30. The same process of revision is discernible in all physiologic measurements. The pulse rate is no longer considered normal at 90, nor is the temperature at 99.6 F. Blood pressure, blood sugar and basal metabolic rates will all be allowed less range in the future. All of these measurements require revision, and revision chiefly downward.

The "normal" that will be selected must be compatible with a long and healthy life. Physicians are beginning to realize that the below average levels are associated with a lower mortality than are the average and therefore are the truly normal levels. This can mean only one thing: Many now acceptable "normal" persons are in reality museums of incipient disease.

It is significant that the pressures now accepted as normal are close to what was once called "hypotension."

It is ironic that since the invention of the sphygmomanometer physicians have attempted to discover some pathologic condition to explain low pressure, the truly normal and ideal range of blood pressure, and have neglected to recognize the ominous character of potential hypertension. As a result, thousands of normal persons are treated for hypotension, and a much larger group in the hypertensive class are given a false sense of security.

Much work is necessary in all fields of blood pressure research. There are necessary more studies of static pressure readings, taken under rigidly standardized conditions, for different social and occupational groups. More important is the need for detailed studies on records continuous over a period of years and on the comparative mortality of persons with various levels of pressure. We hazard the

guess that when the final data are available any changes in the level we have proposed for normal blood pressure will be in the direction of lower limits.

CONCLUSIONS

1. A new and more rational range of normal blood pressure is postulated as the result of (1) a statistical study of 10,883 persons, (2) a study of five to ten year continuous records of 500 persons and (3) an appraisal of mortality at various pressure levels.

2. The normal range of systolic blood pressure for men and women is from 90 to 120 mm. of mercury.

3. The normal range of diastolic blood pressure for men and women is from 60 to 80 mm. of mercury.

4. A normal person attains his mature blood pressure at about adolescence and keeps that range throughout life, except for a slight rise at about the twentieth year.

5. Normal blood pressure does not rise with age. Prehypertensive and hypertensive pressures do rise with age.

6. "Hypotension" is neither a disease nor a disease entity; it is an ideal blood pressure level. In the absence of other findings this is true of pressures that occasionally dip to the level of 80 systolic and 50 diastolic.

7. The commonly described symptoms of the disease called "hypotension" can be ascribed with equal statistical accuracy to any level of blood pressure.

8. Blood pressure should be considered a physiologic measurement in continual diurnal flux, highest during the afternoon, lowest during the early morning hours.

9. The daily and yearly variation of normal blood pressure is from 5 to 10 mm. of mercury.

10. Higher levels of blood pressure show proportionately greater and more erratic yearly variations.

11. Lower levels of blood pressure show smaller and less erratic yearly variations.

12. A blood pressure history is more nearly normal as it shows occasional pressures below 110 systolic and 70 diastolic.

13. A person who has a history of pressures which occasionally dip to the 90 systolic and 60 diastolic level, or even to the upper part of the 80-90 systolic and 50-60 diastolic range, has an added assurance of not becoming hypertensive.

14. A blood pressure history of over 120 systolic and 80 diastolic over a ten year span in a man or woman is pathologic, and is an almost infallible sign of incipient hypertension. Once a pressure is definitely established in this range it seldom if ever will become normal.

15. Transient elevations of blood pressure should not be ignored. They should be suspected of a further, more frequent and possibly permanent rise.

16. Moderately high blood pressures are incipiently hypertensive.

17. Persons with hypertensive heart disease are recruited from persons with incipiently hypertensive blood pressure levels.

18. High blood pressures tend to become even higher, the higher pressures invariably resulting in hyperpiesia.

19. High blood pressure is a long term disease having its genesis at an early age. It is not a disease that suddenly emerges with middle age.

20. Slightly more than 40 per cent of the adult population is either actually or incipiently hypertensive.

21. A study of any normal physiologic measurement must check with mortality data. One of the criteria for the selection of a normal range is that it be compatible with the lowest possible mortality and the longest life span.

22. The mortality rate increases progressively with an increase in systolic or diastolic blood pressure.

23. Persons with low blood pressures have the lowest mortality rate. Those with blood pressures persistently over 120 mm. of mercury systolic and 80 mm. diastolic have a higher mortality rate than those with blood pressures persistently under 120 mm. systolic and 80 mm. diastolic.

Mrs. Mary Neil collected data used in this study over a period of years. Dr. Dudley B. Reed supplied data from the files of the Student Health Service of the University of Chicago. Data from the health service of the West Side Y. W. C. A. were made available by Dr. Rudla Rind. Dr. Louis W. Desprez cooperated in connection with the study of continuous records, and Dr. Anthony N. Trapp secured additional continuous records. Mr. Walter Bittner assisted with the editing of the manuscript. The University of Chicago furnished office space. The statistical labor was performed with the aid of the Works Progress Administration. The project was under the sponsorship of the Institute for Juvenile Research, Dr. Paul L. Schroeder, director. Mr. R. A. Wolff, Mr. Walter Majewski and Miss Florence Duryea assisted with the statistical investigation.

BILIRUBIN AND UROBILIN CONTENT OF BILE OBTAINED BY DUODENAL DRAINAGE

NORMAL VALUES AND VALUES FOR PATIENTS WITH CHOLECYSTITIS

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Study of the bile obtained by means of duodenal drainage in man can give significant data regarding inflammation of the gallbladder. For instance, the presence of desquamative elements originating in the biliary tract (cells; leukocytes) is important evidence of cholecystitis. The difficulty at times consists in deciding whether the elements have come from the gallbladder, the extrahepatic bile ducts or the liver. This applies also to the presence of albumin in the bile. Faulty evacuation of the gallbladder is a sign which is present in cholecystitis; as it is a negative sign and appears in association with other diseases also, it is of much less importance.

Since cholecystitis is a common disease, it is useful to have multiple methods for its diagnosis. For many years I have studied the possibility of making a diagnosis of cholecystitis on the basis of the concentration of the bile pigments bilirubin and urobilin. In 1933 I [1] published my first results, which were later confirmed by Castex and López García.[2]

In this paper I propose to describe first the normal behavior of bilirubin and urobilin in normal bile, clinically and experimentally. Later the same pigments will be considered in relation to pathologic states.

TECHNIC

The bilirubin content was determined as follows: The bile to be tested was mixed with acid alcohol [3] in different proportion (1:10 to 1:50) according to its concentration. Eighteen to twenty-four hours later the mixture was examined with the photometer of Pulfrich, with the filter S66, 613,5, the factor 25 being used as a constant. The difference between the readings for the two drums was multiplied by 25 and by the titer of the dilution. The final result gave in milligrams the concentration of bilirubin per liter. The control readings gave errors not greater than 4 to 5 per cent.

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1. Royer, M.: Les pigments de la bile obtenue par tubage duodénal: Leur importance dans le diagnostic des cholécystites, Presse méd. **41**:74, 1933.

2. Castex, M. R., and López García, A.: La urobilina en el líquido duodenal, Bol. Acad. nac. de med. de Buenos Aires, 1934, p. 128.

3. Acid alcohol is a mixture of 0.4 cc. of concentrated nitric acid, 22 cc. of concentrated hydrochloric acid and 100 cc. of 96 per cent alcohol.

The urobilin content of the bile was measured by means of the method I [4] described in 1928, which is a modification of the one published by Elman and McMaster [5] in 1925, the fluorescence being measured. Later (1932) I [6] modified it for clinical use.

NORMAL STATE IN MAN STUDIED BY DUODENAL DRAINAGE

A study was made by means of duodenal drainage of 25 persons with normal biliary tracts. Only A bile and B bile were considered (table 1); C bile may, for the present purposes, be taken to be like A

TABLE 1.—*Bile Pigments Obtained by Duodenal Drainage from Patients with No Lesions of the Gallbladder*

Case No.	Condition	Bilirubin			Urobilin			Ratio of Bilirubin Increase to Urobilin Increase
		In A Bile, Mg. per Liter	In B Bile, Mg. per Liter	Coefficient of Increase	In A Bile, Mg. per Liter	In B Bile, Mg. per Liter	Coefficient of Increase	
1	Normal	42.0	65	1.5	0.34	0.36	1.0	1.5
2	Typhlitis; constipation	40.0	142	3.0	0.24	0.46	1.9	1.5
3	Cancer of esophagus	131.6	207	1.5	1.12	1.29	1.1	1.3
4	Ovarian insufficiency	28.5	360	12.6	2.10	10.33	4.9	2.5
5	Serofibrinous pleurisy	92.2	423	4.4	0.99	1.53	1.3	3.4
6	Gastritis	60.0	185	3.1	1.12	3.68	3.3	0.9
7	Dyspepsia	121.0	519	4.2	1.53	2.96	1.9	2.2
8	Spondylosis, 2d lumbar vertebra	18.0	125	6.9	1.69	3.36	1.9	3.6
9	Metrosalpingo-oophoritis	10.0	86	8.6	0.34	1.85	5.3	1.6
10	Hyperthyroidism	42.0	108	2.5	1.89	1.53	—0.8	3.3
11	Chronic bronchitis	20.0	105	5.2	0.61	0.81	1.3	4.0
12	Dolichocolon	15.0	165	11.0	1.12	4.88	4.3	2.5
13	Headache	62.0	175	2.8	1.40	1.89	1.3	2.1
14	Gastric lesion	210.0	366	1.7	6.07	9.06	1.4	1.2
15	Hepatitis	80.0	155	1.9	6.07	4.88	—0.7	2.6
16	Epilepsy	150.0	237	1.5	0.89	0.90	1.0	1.5
17	Gastric lesion	65.0	340	5.2	1.89	3.68	1.9	2.7
18	Hyperthyroidism	21.0	250	11.9	0.94	6.07	6.4	1.8
19	Hepatitis	62.0	118	1.9	3.36	4.88	1.4	1.3
20	Hemorrhagic pleurisy	87.0	137	1.5	0.46	0.50	1.1	1.3
21	Hepatitis	37.0	77	2.1	1.29	1.89	1.4	1.5
22	Vertigo	31.0	50	1.6	1.89	1.89	1.0	1.6
23	Fermentative colitis	300.0	975	3.2	3.36	6.07	1.8	1.7
24	Perityphlitis	131.0	425	3.2	0.81	0.88	1.1	2.9
25	Exophthalmic goiter	12.5	430	34.4	0.80	2.44	3.1	11.1

bile. From the data it can be seen that the bilirubin content of B bile was increased in comparison with that of A bile. The difference indi-

4. Royer, M.: La urobilina al estado normal y patologico, Thesis, Buenos Aires, Frescol. y Bindi, 1929; L'urobiline à l'état normal et pathologique: Étude expérimentale et clinique effectuée à l'Institut de Physiologie de la Faculté de Medecine de Buenos-Aires, Paris, Masson & Cie, 1930.

5. Elman, R., and McMaster, P. D.: Studies on Urobilin Physiology and Pathology: I. The Quantitative Determination of Urobilin, J. Exper. Med. **41**: 503, 1925.

6. Royer, M.: Simplification de la méthode du dosage de l'urobiline, Compt. rend. Soc. de biol. **111**:825, 1932; El mesobilirubinógeno como patrón para dosar la urobilina, Rev. Soc. argent. de biol. **8**:489, 1932.

cated the degree of concentration of the bile by the gallbladder. The coefficient of increase is given in the table just mentioned. The urobilin content of B bile was also increased in comparison with that of A bile, but the coefficient of increase was much smaller than that for bilirubin except in case 6. This patient, unfortunately, was not reexamined, but his clinical history indicated that he may have had a lesion of the biliary tract.

These results can be explained if it is admitted that the bile stays a while in the gallbladder and becomes concentrated, owing to the absorption of water by the wall of the gallbladder. It is possible that bile pigments could be absorbed by the wall just as water is. If that is true, in order to explain the results obtained, it is necessary to admit that no bilirubin, or hardly any, is absorbed; this accounts for its high concentration in B bile. It must be admitted that in all cases urobilin is absorbed in greater amount than bilirubin, in order to explain the lower concentration of bilirubin in B bile. One of the reasons for believing that the absorption of urobilin is high in the gallbladder is that, in spite of the loss of water, the concentration of urobilin in B bile is lower than it is in A bile (see data for cases 10 and 15). In these conditions the ratio of the increase of bilirubin to the increase of urobilin will be over 1; in the present group of cases the values ranged from 0.9 to 11.1. An attempt was made to confirm experimentally the previous results.

EXPERIMENTAL STUDY OF BILIRUBIN

A study in the normal dog was made of the ability of both pigments to pass through the wall of the gallbladder. The first observation on this point was made apparently by Aschoff and Bacmeister[7] (1909). They proved that under normal conditions bilirubin can be found in the wall of the gallbladder, owing to the fact that it is passing through the wall. Rous and McMaster[8] (1921) deducted from their experiments on dogs that the bilirubin of the bile is not absorbed by the gallbladder. The objection to their experiments is that the exact amount of bile that entered the gallbladder could not be measured. Neither were they able to prove the presence of bilirubin in the efferent lymphatic ducts of the gallbladder. This last finding was verified by

7. Aschoff, L., and Bacmeister, A.: Die Cholelithiasis, Jena, Gustav Fischer, 1909. Ivy, A. C.: The Physiology of the Gall Bladder, Physiol. Rev. **14**:1, 1934.

8. Rous, P., and McMaster, P. D.: The Concentrating Activity of the Gall Bladder, J. Exper. Med. **34**:47, 1921.

Riegel, Johnston and Ravdin [9] (1932). But in 1924 Sweet [10] found bilirubin in the lymph coming from the gallbladder. Ravdin and Morrison [11] (1931) did not find bilirubin, either in the venous blood or in the lymphatic ducts from the gallbladder.

Riegel, Johnston and Ravdin [9] (1932) have studied the absorption of bilirubin by the gallbladder by employing an excellent technic: A Nélaton catheter is inserted into the gallbladder by way of the hepatic duct, above the point where the ducts from the right and left hepatic lobules make their entrance. Later the hepatic duct is fixed to the catheter in order to keep the latter in the desired place. The other end of the catheter protrudes through a stab wound in the abdominal wall. The operation is performed under aseptic conditions, and the animals live a long time. The authors found it possible to study the animals without resort to anesthesia.

To study the absorption of pigments they introduced into the gallbladder a certain amount of bile with a fixed proportion of bilirubin; a short time later (two to twenty-four hours) the gallbladder was emptied and washed, so that the exact amount of pigment contained therein could be accurately measured. With this technic they observed in 7 of 18 cases a diminution of over 8 per cent (8.7 to 12.9 per cent) in the amount of bilirubin; the average for all the experiments was a diminution of 4.8 per cent. In spite of their own results, the authors stated that they did not believe there was absorption of pigments by the gallbladder. They used bile with such a high concentration of pigments that one wonders how they obtained it. The concentration ranged from 0.32 to 2.2 Gm. per hundred cubic centimeters. All the values were well over what may be considered normal.

The absorption of bile components by the wall of the gallbladder can be detected in various ways: (*a*) by the presence of bile components in the efferent veins and lymphatic vessels of the gallbladder and (*b*) by variations in the composition of the bile inside the gallbladder.

The collection of blood or lymph flowing from the gallbladder is a difficult feat; hence, the second method of study was used.

Method of Collecting Bile.—Dogs anesthetized with a compound of chloral and dextrose were employed in this study. The animal was tied in dorsal decubitus on the operating table. A medial abdominal incision, as large as possible, was made and was extended to the right at its upper end. This last incision was made

9. Riegel, C.; Johnston, C. G., and Ravdin, I. S.: Studies on Gall Bladder Function: VIII. The Fate of Bile Pigment and Cholesterol in Hepatic Bile Subjected to Gall Bladder Activity, J. Exper. Med. **56**:1, 1932.

10. Sweet, J. E.: Gall-Bladder: Its Past, Present and Future, Internat. Clin. **1**:187, 1924.

11. Ravdin, I. S., and Morrison, J. L.: Gallbladder Function: The Contractile Function of the Gallbladder, Arch. Surg. **22**:810 (May) 1931.

at a right angle to the first incision and between clamps so as to avoid hemorrhage. The duodenum was pulled outward gently so as to exteriorize the gallbladder. The portion of the neck of the gallbladder next to the cystic duct was dissected with a blunt instrument to free it from its surroundings. From the neck outward runs a solid whitish band containing vessels. This was dissected away a little so that a ligature could be passed around the neck only. After the ligature was in place the cystic duct was opened a few millimeters with scissors and a urethral catheter was pushed through the incision into the gallbladder. The gallbladder was then emptied, care being taken that the holes of the catheter were in the middle of the gallbladder. The ligature around the neck was then tied securely. The gallbladder was carefully washed out with tepid physiologic solution of sodium chloride until the fluid came away colorless. At times to the washing fluid was added 1 or 2 drops of ammonia water to dissolve any mucus that might be left on the inner wall of the gallbladder. A small amount of bile with a known proportion of pigments was then introduced, and the catheter was closed with a clamp. Meanwhile the abdominal wall was closed, with the catheter left protruding.

After two to eight hours the animal was killed by puncture of the medulla oblongata. The gallbladder was taken out without previous emptying, in order that it might be ascertained that the ligature about the neck was in good condition and that there had been no loss of bile. If it was found that the ligature was not intact, the results were discarded. If the gallbladder was in perfect condition, its content was emptied carefully into a graduated vessel. The gallbladder was opened with scissors, and the bile adherent to the wall was allowed to drip into the container. The total amount of bile was measured. When considered necessary, the gallbladder was washed with saline solution to remove any remaining bile. The aspect of the inner surface of the wall was then examined. If edema was present, the experimental data were considered worthless. For the data to be accepted as reliable, the wall had to be free from hemorrhagic lesions due to the catheterization. Furthermore, the data were accepted as reliable only for those experiments in which half the liquid volume introduced was absorbed. It can readily be understood why a number of the experiments were excluded; in fact, the data for 42 dogs were discarded.

Results.—The results obtained have been divided into two main groups with regard to the concentration of pigments. This separation into two groups is purely arbitrary. It can be seen in table 2 that in 13 experiments the values for pigment varied so that the differences ranged from +9.4 to —23.5 per cent; in 7 experiments the diminution was between — 10.1 and — 23.5 per cent. The average diminution was 10.6 per cent. With bilirubin concentrations of over 200 mg. per liter (table 2), the variations were much smaller; they oscillated between +1.5 and —18.7 per cent. Only once in the 10 experiments was the extreme value of —18.7 obtained. The average of the experiments[1] was a diminution of bilirubin of —3.3 per cent, fairly similar to the value given by Riegel, Johnston and Ravdin (— 4.8 per cent).

All these results lead to the belief that bilirubin is better absorbed when its concentration is low. However, it does not seem possible to establish a law with regard to the absorption and its regulation by the

concentration of pigment; apparently there is no threshold for the absorption.

With the sole purpose of determining whether absorption is greater with low than with high concentrations, some experiments were carried

TABLE 2.—*Bilirubin Content of the Bile in the Gallbladder (Concentrations of Less Than Two Hundred Milligrams per Liter)*

				Introduced Bile			Removed Bile				
					Bilirubin			Bilirubin		Difference	
Dog No.	Weight, Kg.	Time Hr.	Min.	Cc.	Mg. per Liter	Mg.	Cc.	Mg. per Liter	Mg.	Mg.	%
1	14.5	6	20	20	85.0	1.70	14.8	87.5	1.30	−0.40	−23.5
44	12.0	8		15	80.0	1.20	5.9	167.5	1.00	−0.20	−16.6
4	12.0	6	55	18	145.0	1.88	6.0	282.5	1.69	−0.19	−10.1
5	16.5	7	20	15	85.0	1.27	9.0	155.5	1.39	+0.12	+ 9.4
19	15.0	7		13	192.5	2.50	3.0	767.5	2.30	−0.20	− 8.0
20	17.4	7	45	20	55.0	1.10	8.5	105.0	0.89	−0.21	−19.0
21	15.5	8		15	40.0	0.60	6.0	92.5	0.55	−0.05	− 8.3
39	18.5	6	20	25	57.5	1.44	16.0	85.0	1.36	−0.08	− 5.5
42	21.0	7	30	25	25.0	0.62	5.5	92.5	0.51	−0.11	−16.1
46	20.0	7	45	23	30.0	0.69	11.0	60.0	0.66	−0.03	− 4.3
50	17.0	6	50	15	52.5	0.78	6.5	92.5	0.60	−0.18	−23.0
52	26.5	6	25	33	37.5	1.23	16.0	50.0	1.32	+0.09	+ 7.3
57	27.0	7	15	30	42.5	1.27	12.0	85.0	1.02	−0.25	−19.6
Average											−10.6

TABLE 3.—*Bilirubin Content of the Bile in the Gallbladder (Concentrations of More Than Two Hundred Milligrams per Liter)*

				Introduced Bile			Removed Bile				
					Bilirubin			Bilirubin		Difference	
Dog No.	Weight, Kg.	Time Hr.	Min.	Cc.	Mg. per Liter	Mg.	Cc.	Mg. per Liter	Mg.	Mg.	%
8	13.5	7	55	15	345.0	5.33	4.4	1,135.0	4.98	−0.35	− 6.5
47	18.0	6	30	20	240.0	4.80	12.0	392.5	4.71	−0.09	−18.7
12	19.0	8		18	327.5	5.90	9.2	642.5	5.91	+0.01	+0.01
16	12.5	5	45	13	315.0	4.09	6.4	610.0	3.90	−0.19	− 4.6
18	30.0	7	20	22	212.5	4.68	13.1	350.0	4.59	−0.09	− 1.9
24	27.0	7		20	372.5	7.45	11.0	687.5	7.56	+0.11	+ 1.4
27	24.0	7	30	25	407.5	10.18	13.0	792.5	10.29	+0.11	+ 1.0
31	25.0	8		20	355.0	7.10	9.3	752.5	7.00	−0.10	− 1.4
35	16.2	5	45	15	432.5	6.49	7.8	802.5	6.21	−0.28	− 4.3
38	19.0	6	10	20	292.5	5.85	10.7	555.0	5.94	+0.09	+ 1.5
Average											− 3.3

out in which the absorption of different concentrations was tested in the same animal. The animal was prepared according to the method previously described, and a definite amount of bile with a known percentage of pigment was introduced. After three or more hours the gallbladder was emptied and washed many times with tepid physiologic solution of sodium chloride until the solution came away clear. The

total amount of bile was studied. Later, bile with a different concentration of pigment was introduced, and the same procedure was carried out. For each animal bile with a concentration of over 200 mg. per liter and bile with a concentration of less than 200 mg. per liter were

TABLE 4.—*Bilirubin Content of the Bile in the Gallbladder* *

Dog No.	Weight, Kg.	Time Hr.	Time Min.	Introduced Bile: Cc.	Introduced Bile: Bilirubin Mg. per Liter	Introduced Bile: Bilirubin Mg.	Removed Bile: Cc.	Removed Bile: Bilirubin,† Mg.	Difference Mg.	Difference %
62	30.5	2	45	25	37.5	0.94	12.5	0.87	−0.10	−10.5
		2	45	25	255.0	6.37	15.0	6.27	−0.10	− 1.5
65	28.5	3	5	30	92.5	2.77	14.9	2.69	−0.08	− 2.8
		3	5	30	310.0	9.31	17.5	9.32	+0.01	+ 0.1
66	22.5	2	50	20	85.0	1.70	11.6	1.49	−0.21	−12.3
		2	50	20	355.0	7.10	9.5	7.10	0.00	0.0
68	27.0	3		35	410.0	14.52	21.7	14.48	−0.04	− 0.2
		3		35	67.5	2.36	24.0	2.25	−0.11	− 4.6
70	23.0	3	15	22	370.0	8.14	14.2	8.17	−0.03	+ 0.3
		3	15	22	125.0	2.75	14.6	2.70	−0.05	− 1.8
71	21.5	3	5	20	465.0	9.30	11.5	9.30	0.00	0.0
		3	5	20	117.5	2.34	13.1	2.25	−0.09	− 3.8

* Two experiments were carried out in each case, different concentrations of bilirubin being used.

† The concentration of the extracted bile could not be established, because of dilution by the washing fluid.

TABLE 5.—*Urobilin Content of the Bile in the Gallbladder*

Dog No.	Weight, Kg.	Time Hr.	Time Min.	Introduced Bile: Cc.	Introduced Bile: Urobilin Mg. per Liter	Introduced Bile: Urobilin Mg.	Removed Bile: Cc.	Removed Bile: Urobilin Mg. per Liter	Removed Bile: Urobilin Mg.	Difference Mg.	Difference %
1	14.5	6	20	20	3.68	0.070	14.8	1.98	0.029	−0.041	−58.5
44	12.0	8		15	1.80	0.027	5.9	1.94	0.011	−0.016	−59.2
4	12.0	6	55	13	1.35	0.017	6.0	1.48	0.009	−0.008	−47.0
5	16.5	7	20	15	1.20	0.018	9.0	1.18	0.010	−0.008	−44.0
19	15.0	7		13	2.27	0.029	3.0	3.87	0.011	−0.018	−62.0
20	17.4	7	45	20	1.98	0.039	8.5	2.09	0.017	−0.028	−71.7
21	15.5	8		15	7.64	0.114	6.0	6.66	0.039	−0.075	−65.8
39	18.5	6	20	25	4.88	0.122	16.0	4.08	0.065	−0.057	−46.7
42	21.0	7	30	25	1.42	0.035	5.5	2.09	0.016	−0.019	−54.2
46	20.0	7	45	23	1.73	0.039	11.0	1.98	0.021	−0.018	−48.7
50	17.0	6	50	15	3.21	0.048	6.5	4.58	0.029	−0.019	−39.5
52	26.5	6	25	33	1.53	0.050	16.0	2.57	0.041	−0.009	−12.0
57	27.0	7	15	30	1.33	0.039	12.0	2.20	0.026	−0.013	−33.3
Average											−50.2

employed. The animal was later destroyed, and a special investigation was made to detect any remaining pigment in the gallbladder. Six experiments were carried out; in 3 of them the first bile introduced was of low concentration, and in the other 3 the first bile was of high concentration. From table 4 it can be seen that undoubtedly the

absorption is greater when the concentration of bilirubin is less than 200 mg. per liter.

EXPERIMENTAL STUDY OF UROBILIN

Many investigators have studied bilirubin, but I know of no one who has studied the absorption of urobilin by the gallbladder.

In the aforementioned experiments a dose of urobilin was also given. In some cases when the concentration of urobilin was too low a certain amount of crystallized urobilin was added. Tables 5 and 6 show the results obtained, which prove that there is considerable absorption of urobilin by the gallbladder, with averages of —50.2 and —48.4 per cent, respectively. The values were much higher than those obtained for bilirubin.

TABLE 6.—*Urobilin Content of the Bile in the Gallbladder*

				Introduced Bile			Removed Bile				
					Urobilin			Urobilin		Difference	
Dog No.	Weight, Kg.	Time Hr.	Min.	Cc.	Mg. per Liter	Mg.	Cc.	Mg. per Liter	Mg.	Mg.	%
8	13.5	7	55	15	4.31	0.064	4.4	6.07	0.027	—0.037	—57.8
47	18.0	6	30	20	3.87	0.077	12.0	4.31	0.051	—0.026	—33.7
12	19.0	8		18	3.36	0.060	9.2	2.85	0.026	—0.034	—56.6
16	12.5	5	45	13	2.57	0.033	6.4	2.75	0.016	—0.017	—51.5
18	30.0	7	20	22	4.58	0.101	13.1	4.31	0.056	—0.045	—44.5
24	27.0	7		20	1.17	0.028	11.0	0.99	0.011	—0.017	—60.7
27	24.0	7	30	25	1.50	0.037	13.0	1.66	0.022	—0.015	—40.5
31	25.0	8		20	0.94	0.018	9.3	1.02	0.008	—0.010	—55.5
35	16.2	5	45	15	1.48	0.022	7.8	1.59	0.012	—0.010	—45.4
38	19.0	6	10	20	1.73	0.034	10.7	1.98	0.021	—0.013	—38.4
Average											—48.4

PATHOLOGIC CONDITIONS STUDIED BY DUODENAL DRAINAGE IN MAN

A study was also made of patients with cholecystitis, either with or without calculi. The results of duodenal drainage in 70 cases were compiled; these included only the cases in which evacuation of the gallbladder was carried out, that is, those in which B bile was obtained. The cases are divided in three groups in accordance with the proportion of pigments in A and B biles.

In the first group of cases the pigments were in normal proportion. In 41 of the 70 cases (table 7) there was no difference with respect to the amount of pigments. The ratio of the coefficient of increase of bilirubin to the coefficient of increase of urobilin was definitely more than 1; it varied between 1.3 and 8.7, with an average of 2.7.

In the second group of cases the variations in the increases of the urobilin and bilirubin were nearly the same for A and B biles. In 17 cases (table 8) the coefficient of pigmentary increase for B bile was

practically the same for bilirubin and urobilin; in other words, the ratio was 1 or almost 1.

In the third group the increase of urobilin in B bile was greater than the increase of bilirubin. In 12 cases the coefficient of increase of

TABLE 7.—*Normal Proportions of Pigments in Bile of Patients with Lesions of the Biliary Tract*

Case No.		Bilirubin			Urobilin			Ratio of Bilirubin Increase to Urobilin Increase
		A Bile, Mg. per Liter	B Bile, Mg. per Liter	Coefficient of Increase	A Bile, Mg. per Liter	B Bile, Mg. per Liter	Coefficient of Increase	
26	Nonlithiasic cholecystitis	20.0	115	5.7	0.34	0.81	2.4	2.3
27	Nonlithiasic cholecystitis	18.0	167	9.2	1.89	3.68	1.9	4.8
28	Cholelithiasis	18.0	250	13.8	0.81	6.07	7.5	1.8
29	Nonlithiasic cholecystitis	62.0	81	1.3	1.89	1.53	−0.8	2.5
30	Cholelithiasis	10.0	393	39.3	0.84	12.00	14.3	2.7
31	Nonlithiasic cholecystitis	60.0	145	2.4	6.07	9.65	1.5	1.6
32	Nonlithiasic cholecystitis	18.0	87	3.1	0.34	0.58	1.7	1.8
33	Nonlithiasic cholecystitis	62.0	236	3.8	0.81	0.69	−0.8	4.2
34	Nonlithiasic cholecystitis	100.0	212	2.1	0.85	1.12	1.3	1.6
35	Nonlithiasic cholecystitis	63.7	218	3.4	1.12	2.85	2.5	1.3
36	Nonlithiasic cholecystitis	218.0	406	1.8	1.80	2.49	1.3	1.3
37	Nonlithiasic cholecystitis	22.0	204	9.2	0.58	0.88	1.6	5.7
38	Cholegiardiasis	22.0	455	20.6	0.34	3.68	10.8	1.9
39	Nonlithiasic cholecystitis	100.0	450	4.5	1.40	4.88	3.5	1.3
40	Appendicitis; cholecystitis	375.0	755	2.0	1.05	1.40	1.3	1.5
41	Cholecystitis	28.0	200	7.1	0.34	0.64	2.0	3.5
42	Cholecystitis	87.0	262	3.0	1.29	1.89	1.4	2.1
43	Cholecystitis	16.0	100	6.2	0.38	0.69	1.8	3.4
44	Cholelithiasis	10.0	45	4.5	0.59	1.82	3.1	1.4
45	Cholecystitis	35.0	85	2.4	0.97	1.23	1.2	2.0
46	Cholecystitis	72.0	1,000	13.8	0.48	1.85	3.9	3.5
47	Cholelithiasis	57.0	337	5.9	0.81	1.89	2.3	2.5
48	Cholelithiasis	68.0	237	3.4	0.85	2.10	2.4	1.4
49	Cholecystitis	15.0	105	7.0	0.34	1.33	3.9	1.7
50	Cholelithiasis	80.0	670	8.3	1.89	2.10	1.1	7.5
51	Cholecystitis	300.0	750	2.5	9.06	12.04	1.3	1.9
52	Cholelithiasis	22.0	86	3.9	0.47	0.99	2.1	1.8
53	Cholecystitis	13.0	262	20.1	0.46	1.07	2.3	8.7
54	Cholecystitis	83.0	850	10.2	0.99	3.68	3.7	2.7
55	Cholecystitis	20.0	85	4.2	1.11	2.10	1.8	2.3
56	Cholecystitis	110.0	185	1.6	4.08	4.88	1.1	1.4
57	Cholecystitis	15.0	62	4.1	0.81	0.89	1.1	3.7
58	Cholecystitis	55.0	160	2.9	2.57	4.88	1.8	1.5
59	Cholecystitis	25.0	60	2.4	0.81	1.40	1.7	1.4
60	Cholecystitis	10.0	115	11.5	1.76	5.22	2.9	3.9
61	Cholecystitis	50.0	95	1.9	0.34	0.46	1.3	1.4
62	Cholecystitis	30.0	75	2.5	0.81	1.53	1.8	1.3
63	Cholecystitis	35.0	100	2.8	0.69	0.89	1.3	2.1
64	Cholecystitis	20.0	75	3.7	0.81	1.20	1.4	2.6
65	Cholecystitis	21.2	362	17.0	0.38	0.81	2.1	8.1
66	Cholecystitis	62.5	150	2.4	0.81	0.69	−0.8	3.2
	Average							2.7

urobilin was larger than that of bilirubin. In these cases the ratio was, of course, less than 1. This value is smaller the larger the increase of urobilin with respect to the increase of bilirubin (table 9).

TABLE 8.—*Data for Patients with Cholecystitis Who Showed a Similar Concentration of Bilirubin and Urobilin in A and B Biles*

Case No.	Condition	Bilirubin			Urobilin			Ratio of Bilirubin Increase to Urobilin Increase
		A Bile, Mg. per Liter	B Bile, Mg. per Liter	Coefficient of Increase	A Bile, Mg. per Liter	B Bile, Mg. per Liter	Coefficient of Increase	
67	Cholelithiasis	137.0	175	1.3	1.87	2.49	1.3	1.0
68	Cholecystitis	68.0	103	1.5	1.66	2.49	1.5	1.0
69	Cirrhotic jaundice	38.0	68	1.7	0.46	0.82	1.7	1.0
70	Cholecystitis	62.0	102	1.6	1.69	2.96	1.7	0.94
71	Cholecystitis	259.0	891	3.4	0.90	3.21	3.5	0.97
72	Cholecystitis	93.0	193	2.1	0.46	0.99	2.1	1.0
73	Cholecystitis	40.0	135	3.4	0.94	3.36	3.5	0.97
74	Nonlithiasic cholecystitis	72.0	400	5.5	1.29	6.66	5.1	1.07
75	Nonlithiasic cholecystitis	53.0	115	2.1	0.81	1.53	1.9	1.10
76	Nonlithiasic cholecystitis	15.0	75	5.0	0.34	1.53	4.5	1.11
77	Cholecystitis	12.0	120	10.0	0.51	4.88	9.5	1.04
78	Cholelithiasis	50.0	141	2.8	0.69	2.10	3.0	0.93
79	Nonlithiasic cholecystitis	21.0	56	2.6	0.34	0.89	2.8	0.93
80	Nonlithiasic cholecystitis	125.0	340	2.7	1.25	3.68	2.9	0.93
81	Angiocholecystitis	31.0	87	2.8	0.58	1.69	2.9	0.96
82	Cholecystitis	15.0	45	3.0	0.38	1.29	3.3	0.91
83	Cholelithiasis	12.4	74	5.9	1.53	8.05	5.2	1.13

TABLE 9.—*Data for Patients with Cholecystitis Who Showed a Greater Increase of Urobilin over Bilirubin in B Bile Than in A Bile*

Case No.	Condition	Bilirubin			Urobilin			Ratio of Bilirubin Increase to Urobilin Increase
		A Bile, Mg. per Liter	B Bile, Mg. per Liter	Coefficient of Increase	A Bile, Mg. per Liter	B Bile, Mg. per Liter	Coefficient of Increase	
84	Nonlithiasic cholecystitis	15	32.0	2.1	0.58	1.76	3.0	0.7
85	Nonlithiasic cholecystitis	22	65.0	2.9	0.58	2.49	4.2	0.67
86	Nonlithiasic cholecystitis	60	90.0	1.5	0.81	3.68	4.5	0.3
87	Cholecystitis; pericholecystitis	15	32.0	2.1	0.34	0.82	2.4	0.8
88	Nonlithiasic cholecystitis	38	156.0	4.1	1.29	6.07	4.7	0.8
89	Cholelithiasis	32	120.0	3.5	1.12	6.07	5.4	0.6
90	Nonlithiasic cholecystitis	67	137.0	2.0	1.12	4.88	4.3	0.46
91	Nonlithiasic cholecystitis	23	50.0	2.2	0.75	3.68	4.7	0.46
92	Cholelithiasis	30	70.0	2.3	1.12	2.96	2.6	0.88
93	Cholecystitis	74	155.0	2.1	0.94	2.75	2.9	0.72
94	Cholecystitis	65	123.5	1.9	0.46	1.02	2.2	0.86
95	Cholecystitis	65	140.0	2.1	1.05	4.88	4.6	0.47

TABLE 10.—*Pigments in Bile Obtained After Cholecystectomy*

Hours	Bilirubin, Mg. per Cc.	Urobilin, Mg. per Cc.	Ratio of Bilirubin to Urobilin
9	2.4	0.005	480
11	1.2	0.0008	1,500
13	1.2	0.0006	2,000
15	1.1	0.00072	1,666
17	1.2	0.00066	1,818
20	0.9	0.0009	1,000
7	0.8	0.00072	1,111
9	1.1	0.00062	1,935

TABLE 11.—*Concentration of Urobilin and Bilirubin When Cecal Material Was Introduced into the Gallbladder*

Dog No.	Weight, Kg.	Time		Bilirubin			Urobilin		
		Hr.	Min.	Introduced, Mg.	Removed, Mg.	Difference, %	Introduced, Mg.	Removed, Mg.	Difference, %
74	12.8	3	40	1.88	1.69	—10.1	0.18	0.29	+61.1
76	15.5	4	10	4.09	3.68	—10.0	0.28	0.34	+21.4
77	14.0	2	55	3.90	3.64	— 6.6	0.37	0.46	+24.3
79	14.5	3	45	1.27	1.12	—11.0	0.22	0.31	+40.9
80	16.0	3	55	1.70	1.62	— 4.7	0.45	0.61	+35.5

COMMENT

Of the aforementioned groups of cases in which duodenal drainage was carried out, the most interesting was no doubt the third group, in which the concentration of urobilin was increased more than that of bilirubin. As it is known that the absorption through the wall of the gallbladder is higher for urobilin than it is for bilirubin, one is compelled to admit that in order for this to occur there must be local production of urobilin. This production can occur only at the expense of bilirubin, surely in much the same way as stercobilin is formed in the intestine, that is, by bacterial action. It must be remembered that no one has ever demonstrated the formation of urobilin experimentally in the body apart from this bacterial action. Then, in order to accept the theory of local formation of urobilin in the gallbladder, there must be bacteria in the bile. The patients with this type of bile therefore have cholecystitis.

The second group of patients had bile of a type intermediate between the normal and the obviously pathologic. To explain the fact that the increase in the urobilin concentration was equal to the increase in the bilirubin concentration, the theory of local formation of urobilin must again be accepted. The considerable absorption of urobilin by the wall of the gallbladder with respect to that of bilirubin must be compensated for by the formation of the same amount as is absorbed in order that the coefficients of increase may remain the same. Again, one must admit that the bile of these patients contained bacteria, and, as a consequence, the patients had cholecystitis.

In spite of the fact that it was obtained from patients with cholecystitis, the bile obtained in the first group of cases did not differ from normal bile. This can be explained as follows: In the first place, there may be inflammation of the gallbladder without the production of any modification in the bile contained in it. Second, the bile may contain bacteria but not the organisms capable of transforming bilirubin into urobilin. Third, the bile may contain bacteria and may show local production of urobilin, but the amount produced is smaller than the amount absorbed.

Heretofore it has been taken for granted that the ratio of bilirubin to urobilin in bile from the liver is always the same. B bile may be considered to be the result of the mixture of hepatic bile secreted during a fairly long period while A bile represents the secretion of only a short period. As I pointed out in 1933, the relation between the two pigments is not always the same. In a case in which cholecystectomy was performed the results (shown in table 10) indicated a considerable variation in the bilirubin-urobilin ratio. In spite of the great absorption of urobilin by the wall of the gallbladder, however, information derived from study of the pigment is of great importance.

In an attempt to reproduce experimentally the formation of urobilin in the gallbladder, a series of experiments was carried out on dogs with the aforementioned technic. The only difference was that when bile was introduced into the gallbladder, several drops of cecal content was also introduced. The cecal content was obtained from the same animal by puncture of the cecum with a large needle. After several hours the animal was killed, and an examination similar to that already described was made. The results recorded in table 11 show clearly that in these animals a certain amount of urobilin was produced in the gallbladder and that it could have come only from the bilirubin.

SUMMARY

The concentrations of bilirubin and urobilin are higher in B bile than in A bile.

The increase in concentration of urobilin is normally lower than that of the bilirubin. This is due to the fact that only a small amount of bilirubin is absorbed by the wall of the gallbladder, while urobilin is absorbed in surprisingly large amounts.

In a certain number of cases of cholecystitis (41.4 per cent of our cases) the production of urobilin in the gallbladder can be observed. This fact explains why the ratio of increase of bilirubin to increase of urobilin is lower than the normal ratio. Data in this regard can be of use in making a differential diagnosis of inflammation of the gallbladder.

"CARDIAC CIRRHOSIS" OF THE LIVER

A CLINICAL AND PATHOLOGIC STUDY

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The term "cardiac cirrhosis" is used to denote various conditions. According to some authors, the term signifies any type of hepatic fibrosis occurring in a patient with cardiac disease; to others it signifies that the hepatic fibrosis is due to congestive failure, while some authors reserve the application of the term for cases in which cirrhosis of the liver due to congestive failure is responsible for clinical manifestations of portal obstruction, such as recurrent ascites or splenomegaly. Thus, the varied usages of the term imply (1) a simple coexistence of hepatic fibrosis and cardiac disease, (2) a causal interrelation between the two anatomic conditions or (3) a causal morphologic interrelation which results in clinical manifestations of portal obstruction.[1]

These different connotations of the term have been responsible in part for the conflicting statements in the literature. There has also been considerable discussion as to the site and nature of the fibrosis in the liver; certain authors have stated that the apparent fibrosis represents only a simple condensation of reticular fibers almost always confined to the centers of the lobules, and other investigators have attributed the changes to active proliferation of fibroblasts. Confronted in certain cases of congestive failure with the question of the presence of cardiac cirrhosis and with a paucity of pertinent available information, we undertook the following investigation of an unselected series

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1. Gerlach, W.: Die Kreislaufstörungen der Leber, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 5, pt. 1, p. 71. Roessle, R.: Entzündungen der Leber, ibid., p. 243.

of consecutive cases in which autopsy was done in order to learn: (1) the incidence of hepatic fibrosis in all cases of congestive heart failure; (2) the types and degrees of hepatic fibrosis in cases of congestive failure of varying duration; (3) the difference between these findings and those in cases in which there is no congestive failure, and (4) the incidence of hepatic fibrosis in cases of congestive failure compared with that in patients with disease of the biliary tract.

Such a comparison of the incidence and degrees of the various types of hepatic fibrosis in cardiac and noncardiac pathologic conditions should indicate the significance of congestive failure as a factor in the causation of cirrhosis of the liver.

TABLE 1.—*Incidence of Fibrosis of the Liver in Two Thousand Unselected Cases*

Type of Fibrosis	Nature of Disease	Degree of Fibrosis			Total No. of Cases
		+	++	+++	
Portal*	Chronic passive congestion	29	5	6	40
	Disease of the biliary tract	31	1	6	38
	Both chronic passive congestion and disease of the biliary tract	5	2	1	8
	Neither	80	19	27	126
Central	Chronic passive congestion	13	9	2	24
	Both chronic passive congestion and disease of the biliary tract	1	1	0	2
Combined portal and central	Chronic passive congestion	7	6	1	14
	Disease of the biliary tract	1	0	0	1
	Both chronic passive congestion and disease of the biliary tract	1	1	1	3
Biliary	Disease of the biliary tract	23	10	4	37
	Both chronic passive congestion and disease of the biliary tract	0	2	0	2
Diffuse	Chronic passive congestion	1	0	1	2
	Disease of the biliary tract	0	2	2	4
	Neither	0	2	0	2
					303

* Since slight increases in fibrous tissue in the portal areas cannot be detected with absolute certainty, only those livers with definite degrees of fibrosis in these areas are included.

METHODS

Two thousand consecutive autopsy protocols were examined, and the following four groups of cases were selected for further study in order to ascertain the interrelation of chronic passive congestion, hepatic fibrosis and certain other possible factors in the production of an increase of connective tissue in the liver. Cases of chronic passive congestion, cases of disease of the biliary tract, cases in which both conditions were present and cases in which neither condition was present were studied as four separate groups. Patients were considered to have had chronic passive congestion only if definite edema of the dependent parts had been present. Patients were considered to have had disease of the biliary tract if there was postmortem evidence of chronic cholecystitis, cholelithiasis, carcinoma of the ducts, obstructing

carcinoma of the head of the pancreas or of the gallbladder or infection of the biliary tract.

The incidence of fibrosis in each of the four groups was ascertained in the following manner: Cases in which, according to the postmortem protocol, there was a definite increase in fibrous tissue were selected for further study. In each instance the microscopic examination was repeated in order to verify the finding of increased fibrous tissue, and if the increase was questionable the case was discarded from this category. For this reason approximately one quarter of the cases in which the presence of periportal fibrosis had been recorded were excluded. Since no case in which the pathologist had not observed increased hepatic fibrosis was included in this group, any error involved in the method would lead to too low rather than too high a percentage. As a final check on the accuracy of the estimates, slides of liver tissue classified as (1) normal and (2) showing increased fibrosis (particularly specimens in which the fibrosis was characterized as 1 plus) were reexamined by another method. At the suggestion of Dr. Monroe Schlesinger a group of such slides was taken, six arbitrary areas were marked, and an observer unacquainted with the classification of the cases estimated the percentage of each field occupied by central and by periportal fibrosis. The results were in accord with those previously recorded.

The microscopic pathologic changes in all cases in which increased hepatic fibrosis was found were classified according to five general types: (1) periportal fibrosis, (2) biliary fibrosis, (3) central fibrosis, (4) patchy or diffuse fibrosis and (5) combined portal and central fibrosis. The term biliary cirrhosis was applied only to specimens showing proliferation of the bile ducts, inflammatory cells and fibrosis about the bile ducts. (Some of the specimens classified as showing periportal fibrosis may conceivably have been representative of the end stage of biliary cirrhosis. They lacked, however, one important criterion for this diagnosis, namely, inflammatory cells.) Each of these types of fibrosis was subdivided into groups according to the degree of pathologic change. Slight degrees of increase in central fibrous tissue signified any fibrosis around the central vein which clearly could not be ascribed to condensation of the reticulum. For practically all the specimens aniline blue connective tissue stain was used, and if this disclosed collagen fibrils pathologic fibrosis was considered to be present. Because of the normal variation in the amount of periportal connective tissue, particularly the increase usually found in old persons, only instances in which the increase was unquestionable were included. In any given case the degree of increase represents the average finding in several slides; in some fields the increase in fibrous tissue was less than the average; in others, it was greater. The same considerations apply to specimens classified as showing 2 plus or 3 plus fibrosis. The 3 plus

group included specimens in which more than half of the parenchyma was replaced by fibrous tissue and the liver showed gross pathologic change, such as hobnailed surface, atrophy or the appearance of hepar lobatum. Of the specimens showing periportal involvement, 40 showed advanced portal, or Laennec's, cirrhosis. The group designated as 2 plus showed intermediate degrees of increase in either central or periportal fibrosis; the connective tissue extended out into the parenchyma of the lobules.

RESULTS

The ages of all patients with increase in the various types of fibrosis was ascertained; it was found that the fibrosis could not be

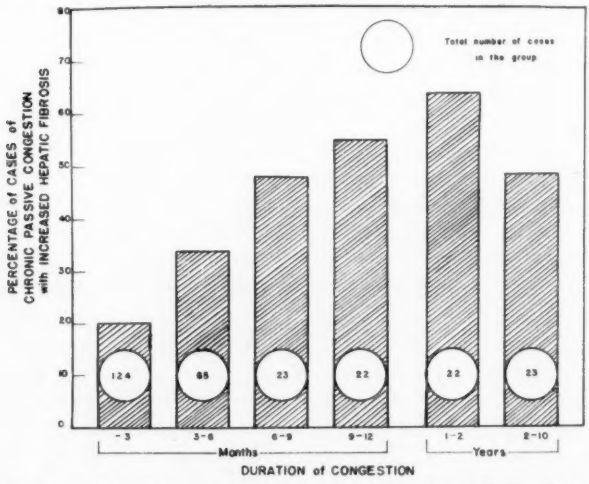

Fig. 1.—Relation between the duration of congestive failure and the incidence of increased hepatic fibrosis. It is shown that the longer the duration of congestive failure, the higher the incidence of increased hepatic fibrosis.

attributed to the aging process. Of the 2,000 cases there was unquestionable increase of connective tissue in the liver in 303, or 15 per cent; the average age of the patients in this group was 56 years.

1. The first group consisted of cases in which a diagnosis of chronic congestive heart failure was made ante mortem. Of the 2,000 cases, 286, or 14.3 per cent, were in this group. The average age of the 286 patients at death was 50.3 years, as compared with the average of 50.5 years for the entire group. The duration of heart failure, ascertained as accurately as possible from the clinical histories, was divided into several periods, and the number of cases in each period was plotted (fig. 1). Of the 286 cases of chronic passive congestion,

increased hepatic fibrous tissue was found in 95, or 33 per cent (table 2). A study was made of this group of 95 cases to ascertain the following facts: (1) the type and degree of fibrosis (table 2); (2) the relation between the incidence of fibrosis and the duration of congestive failure (fig. 1); (3) the relation between the degree of fibrosis and the duration of congestive failure (fig. 2), and (4) the incidence of ascites, anemia and jaundice (table 3).

TABLE 2.—*Types and Degrees of Pathologic Increase of Connective Tissue in the Liver in Two Hundred and Eighty-Six Cases of Chronic Congestive Heart Failure*

Type of Fibrosis	Degree of Fibrosis			Total No. of Cases
	+	++	+++	
Portal	34	7	7*	48
Central	14	10	2	26
Combined portal and central	8	7	2	17
Biliary	0	2	0	2
Diffuse	1	0	1	2
				95

* The appearance of the liver in these 7 cases of extreme portal fibrosis was typical of that seen in Laennec's cirrhosis.

TABLE 3.—*Comparison of Incidence of Ascites, Jaundice and Anemia in All Cases of Chronic Passive Congestion with That in Cases of Chronic Passive Congestion Plus Hepatic Fibrosis*

	A. Cases of Chronic Passive Congestion Plus Hepatic Fibrosis, Percentage	B. All Cases of Chronic Passive Congestion, Percentage
Ascites*	59	50
Jaundice	20	16
Anemia†	14	18

* Ascites was considered present when 50 cc. or more of fluid was found in the peritoneal cavity at postmortem examination.

† Anemia was considered present when the red blood cell count was less than 4,000,000 per cubic millimeter or the hemoglobin value was 60 per cent or less.

It was apparent that the incidence of fibrosis was higher in cases of chronic passive congestion than in the entire unselected series; consequently it became of interest to ascertain whether minimal changes in the liver were largely responsible for this difference. As is shown in figure 3, the distribution of the various degrees of fibrosis was approximately the same. The presence or absence of anemia, jaundice or ascites was ascertained in the 286 cases of chronic passive congestion in order to learn the frequency with which these signs were present (table 3).

2. The second group consisted of cases in which there was postmortem evidence of disease of the biliary tract. Three hundred and eighty-

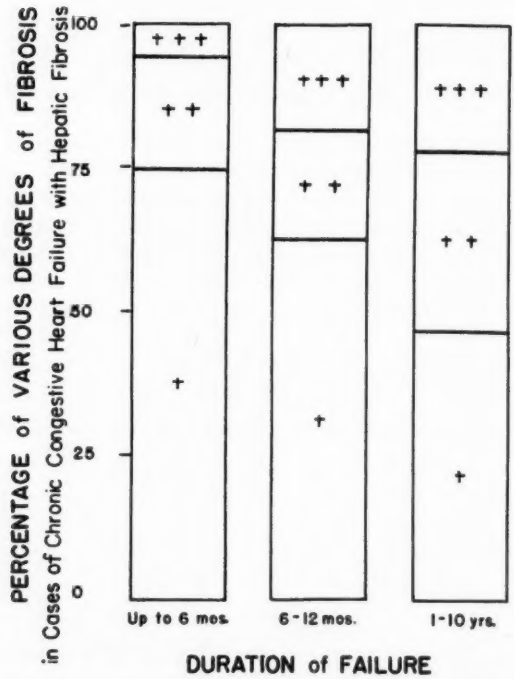

Fig. 2.—Relation between the incidence of the various grades of cirrhosis and the duration of congestive failure. It is shown that the longer the duration of congestive failure, the greater the proportion of the more severe grades of cirrhosis.

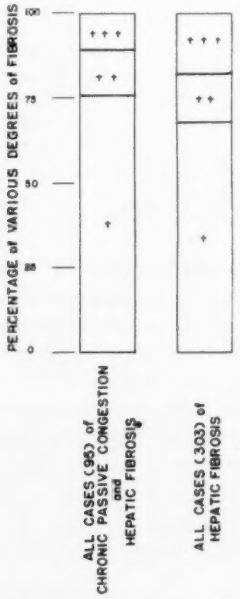

Fig. 3.—Incidence of various degrees of fibrosis. It is shown that the increased incidence of hepatic fibrosis in cases of congestive failure is not due to a preponderance of minimal degrees of fibrosis.

seven cases, or 19.4 per cent of the 2,000, were in this category; the average age of the patients in this group at the time of death was 60 years. In 95 cases there was a definite increase in connective tissue; the incidence of increased fibrosis was 24 per cent.

3. The third group consisted of cases in which increased hepatic fibrosis was found in the absence of both chronic passive congestion and disease of the biliary tract. One hundred and twenty-eight cases were in this category.

From the foregoing data, the extent to which fibrosis of the liver could be correlated with chronic passive congestion of the heart and also with disease of the biliary tract was ascertained. The incidence of increased hepatic fibrosis in the cases of chronic passive congestion was 33 per cent, as compared with an incidence of 12 per cent in the 1,714 cases in which congestive failure was absent. The difference between the two incidences of 33 per cent and 12 per cent is 21 per cent, and the standard error of this difference is 2.9; the difference is therefore convincing. In 15 cases in which fibrosis was found, pathologic conditions of the biliary tract and chronic passive congestion coexisted. It might be argued that the pathologic condition of the biliary tract was responsible for fibrosis of the liver in these cases and for the high incidence of fibrosis in the cases of chronic passive congestion. If, however, these 15 cases are excluded, hepatic fibrosis which could not be ascribed to disease of the biliary tract was found in 28 per cent of the remaining cases of chronic passive congestion, an incidence almost equally significant.

COMMENT

Of the 286 cases in which death was due to congestive heart failure, increased hepatic fibrous tissue was found in one third, which was approximately three times the incidence found in the remaining 1,714 cases in which congestive failure was absent. The incidence of the various degrees of fibrosis was, in general, similar in both groups of cases (fig. 3). Further, the incidence of fibrosis in cases of chronic passive congestion increased with the duration of congestive failure, and the more severe grades were found in cases in which the illness was of longest duration. Thus, the causal significance of chronic passive congestion in the production of hepatic fibrosis was emphasized by the increasing incidence and severity of the fibrosis with increasing duration of congestive heart failure (figs. 1 and 2). The only type of increase of fibrous tissue peculiar to this group of cases of cardiac decompensation was central fibrosis, for, with a single exception, no instance of central fibrosis was found among the 1,714 cases in which autopsy failed to disclose congestive failure.

It should be noted that other types of fibrosis were also observed in the cases of chronic passive congestion. Indeed, the incidence of each of the various kinds of fibrosis (except biliary fibrosis) was higher in the cases of congestive failure than in the remaining 1,714. Of particular interest was the finding of increased periportal connective tissue in 23 per cent of the 286 cases of congestive failure, as compared with 9 per cent of the 1,714 cases in which chronic passive congestion was absent. The occurrence of only 2 instances of biliary cirrhosis in the entire group of cases of chronic passive congestion indicates the absence of any etiologic relation between these two conditions, 2 cases being within the expected incidence in 95 random autopsies.

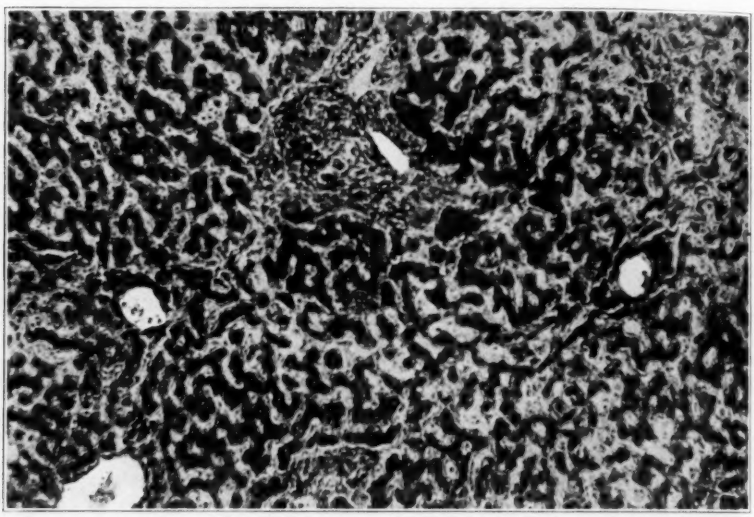

Fig. 4.—Photomicrograph of a section of the liver. Just above the center is shown an enlarged portal space, with a definite increase in fibrous tissue, some round cell infiltration and extensions of fibrous tissue into the liver substance. At the lower edge of the center there is another portal space with no fibrotic increase. Two central veins may be seen, one on either side, each surrounded by a small, dense ring of fibrous tissue. A third central vein, at the lower left corner, shows a thin ring of fibrosis, which stands out with the aniline blue stain. At the time of death there was no necrosis about the central veins. This condition was tabulated as portal fibrosis 1 plus, central fibrosis 1 plus.

Since it is commonly accepted that disease of the biliary tract is an important cause of hepatic fibrosis, it was of interest to learn that congestive failure is of comparable etiologic significance.

In addition to the 48 cases of congestive failure in which there was only portal fibrosis and the 26 cases in which there was only central

fibrosis, central and portal fibrosis coexisted in 18 instances and were associated with congestive heart failure in all but a single case. This suggests that chronic passive congestion, with resulting anoxemia, may increase the susceptibility of the hepatic tissue to injury in the portal as well as in the central area. In the process of classification, when the increase in portal connective tissue was questionable or when the fibrosis was confined to one area in the liver, the specimen was not classified as showing portal fibrosis. The incidence of portal fibrosis in this series is therefore of increased significance. In 7 cases the severe form of portal cirrhosis, or Laennec's cirrhosis, was present. That more

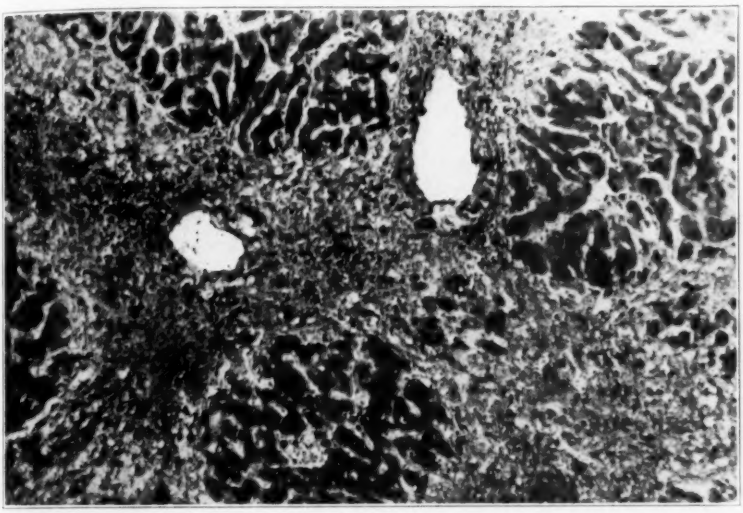

Fig. 5.—Photomicrograph of a section of the liver. Two dilated central veins are seen, with destruction of liver cells and hemorrhage extending from one to another. There is a ring of dense fibrous tissue about each of the central veins, clearly demarcated by the aniline blue stain. Two normal portal spaces are seen, one in the center on the bottom of the photograph, the other to the right of the larger central vein. Loss of liver parenchyma is marked in central areas, and there is a sharp separation from the relatively unaffected portal areas. The condition was tabulated as central fibrosis 3 plus.

instances of this advanced form were not found may well be due to the relatively short duration of life once congestive failure of severe enough degree to cause hepatic damage has occurred. The characteristics of portal cirrhosis in cases of congestive failure are not peculiar.

Our findings are in accord with those of Piéry,[2] who concluded that stasis of blood predisposes the liver to cirrhosis by the action of toxins and inflammatory processes. The work of Bolton [3] is of interest in this connection. He produced passive venous congestion of the liver experimentally and observed not only widespread degeneration of the liver cells about the central hepatic veins, but an "inflammatory infiltration of the portal canals leading to some degree of cirrhosis." Lambert and Allison,[4] however, concluded that chronic passive congestion never leads to the development of cirrhosis of the usual portal or nodular type. They found an active new growth of connective tissue in only 2 of 112

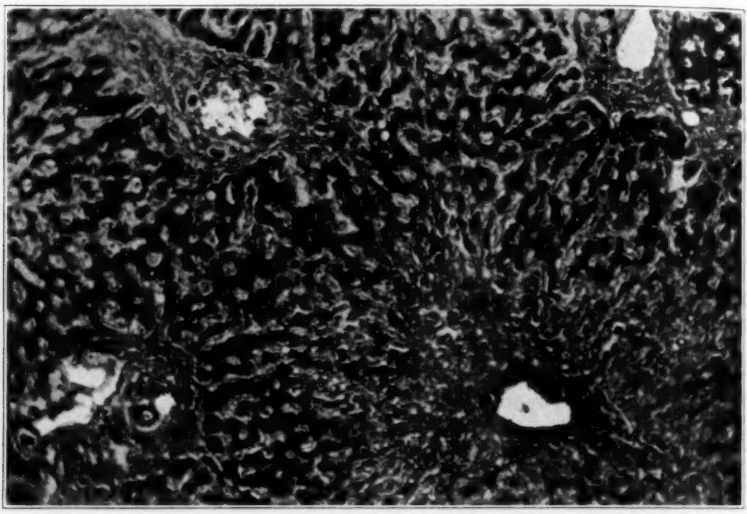

Fig. 6.—Photomicrograph of a section of the liver. There are three portal spaces, one in each upper corner and one in the lower left corner. These show a definite increase in fibrous tissue, with proliferation of the bile ducts and extensions of connective tissue into the surrounding parenchyma. The central vein in the right lower corner is surrounded by a ring of connective tissue, with fibrils extending out into the liver parenchyma. Areas of congestion and hemorrhage are not sharply outlined. This condition was classified as portal fibrosis 2 plus, central fibrosis 2 plus.

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2. Piéry, M.: Pathogénie de la cirrhose cardiaque: Stase sanguine et sclérose du foie; étude clinique et anatomopathologique, Arch. gén. de méd. **4**:582 and 714, 1900.

3. Bolton, C.: The Pathological Changes in the Liver Resulting from Passive Venous Congestion Experimentally Produced, J. Path. & Bact. **19**:258, 1914.

4. Lambert, R. A., and Allison, B. R.: Types of Lesions in Chronic Passive Congestion of the Liver, Bull. Johns Hopkins Hosp. **27**:350 (Dec.) 1916.

cases of chronic passive congestion; in these 2 only the central portions of the lobules were involved.

Central cirrhosis results from the growth of fibrous tissue about the central vein, due to organization of hemorrhage or to metabolic changes occurring as a result of repeated or prolonged anoxemia.[5] Simple condensation of the reticulum about the central vein is not included in this diagnosis. In some instances in our series the central fibrosis extended from one central area to another, demarcating the portal lobules; in others it extended irregularly toward the periphery and resulted in an irregular scar. These changes have been clearly reproduced experimentally by Zimmerman and Hillsman.[6] Moschcowitz[7] has suggested that the increase in fibrosis in the central areas may be secondary to sclerosis of the central veins due to marked hepatic venous congestion.

In 8 cases the condition was designated "patchy or diffuse fibrosis" (table 1). In only 2 of these was there chronic passive congestion. Emboli, as well as bacterial endocarditis[8] and other conditions, are recognized as a cause of this type of fibrosis.[8] Advanced patchy fibrosis is, however, usually a result of acute yellow atrophy or of syphilis, as in hepar lobatum.

Clinical cardiac cirrhosis signifying extreme fibrosis which clearly results from chronic passive congestion and which causes evidences of portal obstruction does occur, but is rare. Of the 286 cases of congestive failure, there were only 15 in which there was marked (not necessarily predominant) ascites requiring abdominal paracentesis. In 6 of these 15 cases cirrhosis of the type caused only by chronic passive congestion, namely, central fibrosis, was demonstrable at autopsy. Although increased fibrous tissue was found in the majority of cases in which heart failure has existed for nine months or more, preponderant ascites was not necessarily present. The association of anemia or jaundice with congestive failure was not closely correlated with the pathologic increase of connective tissue observed at autopsy; these factors are consequently of no value in diagnosing hepatic cirrhosis clinically. Morphologic evidence of increased fibrosis of the liver was seen in all of the 6

5. Rich, A. R.: The Pathogenesis of the Forms of Jaundice, Bull. Johns Hopkins Hosp. **47**:338 (Dec.) 1930.

6. Zimmerman, H. M., and Hillsman, J. A.: Chronic Passive Congestion of the Liver: An Experimental Study, Arch. Path. **9**:1154 (June) 1930.

7. Moschcowitz, E.: Phlebosclerosis of the Hepatic Veins as Associated with Chronic Passive Congestion of the Liver and Cardiac Cirrhosis: Preliminary Report, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman, New York, International Press, 1932, vol. 2, p. 857.

8. Mallory, F. B.: Cirrhosis of Liver (Shattuck Lecture), New England J. Med. **206**:1231 (June 16) 1932.

cases in which recurrent ascites was present and heart failure had existed for two years or more.

From these studies it would seem that cardiac cirrhosis signifying morphologic increase in connective tissue in the liver consequent to congestive failure is present in approximately 50 per cent of all patients who have had congestive failure nine months or more. While central cirrhosis is characteristic of congestive failure and does not occur in patients with disease of the biliary tract, it would appear that other portions of the liver are also more susceptible to injury in patients with chronic passive congestion. Thus, 48 instances of uncomplicated periportal fibrosis were encountered in the group of 286 cases of chronic passive congestion, which contrasts with an expectancy of only 26 cases if congestive failure were not a contributory factor. The occurrence of 22 additional cases in which there was definitely increased fibrosis of both the central and the portal areas is further evidence of an increased susceptibility of the portal areas to injury under such circumstances.

Excluding the cases in which there was increased connective tissue in both the central and the portal areas, the incidence of portal fibrosis in the 286 cases of congestive failure was 17 per cent, as compared with an incidence of central fibrosis of 9 per cent. The significance of alcoholism [9] as a contributory factor could not be accurately appraised, although increased consumption of alcohol was not apparent in the records of the patients with congestive failure.

By the foregoing evidence the meaning of the term cardiac cirrhosis is clarified. In the morphologic sense of increased fibrosis being due to chronic passive congestion, one may state that the livers of the majority of patients who have suffered from even mild congestive failure for nine months or more show increased fibrosis, central or portal or both.

The determination of whether cardiac cirrhosis in the clinical sense of increased fibrosis causing clinical manifestations is present must be based on clinical evidence. If there is preponderant ascites, if there is marked elevation of the venous pressure but the liver is not palpable and particularly if the spleen is palpable, clinical cardiac cirrhosis may be assumed to exist. The reverse situation, however, was more frequently present in our series of cases. The liver was enlarged and ascites was present. In such cases, though increased fibrous tissue was present and the surface of the liver generally was nontender and sometimes somewhat irregular, the dilatation of the sinusoids led to an increase in the size of the liver. The liver of a patient with a condition clinically diagnosed as cardiac cirrhosis may show portal or central fibrosis, singly or in combination, or diffuse patchy fibrosis.

9. Moon, V. H.: Experimental Cirrhosis in Relation to Human Cirrhosis, Arch. Path. **18**:381 (Sept.) 1934.

SUMMARY

An investigation of an unselected series of 2,000 consecutive cases in which autopsy was performed was undertaken in order to learn the incidence, types and degrees of hepatic fibrosis in cases of congestive failure and to make a comparison of these findings with those in cases in which congestive failure was absent.

Of the 286 cases of chronic passive congestion, there was an increase of hepatic fibrous tissue in 95, or 33 per cent. In 1,714 cases in which chronic passive congestion was absent the incidence of hepatic fibrosis was 12 per cent. The causal significance of chronic passive congestion in the production of hepatic fibrosis was emphasized by the increasing incidence and severity of the fibrosis with increasing duration of congestive heart failure. The incidence of each of the various kinds of fibrosis except biliary fibrosis was higher in 286 cases of congestive failure than in the remaining 1,714. The only type of increase in connective tissue peculiar to the cases of cardiac decompensation was central fibrosis, for, with a single exception, no instance of central fibrosis was found in 1,714 cases in which autopsy disclosed an absence of congestive failure. Of particular interest was the finding of increased periportal connective tissue in 23 per cent of the 286 cases of congestive failure, as compared with an incidence of 9 per cent in the 1,714 cases in which chronic passive congestion was not present. While central fibrosis was found only in cases of chronic passive congestion, portal fibrosis also was found in a larger percentage of such cases than in cases in which chronic passive congestion was absent. This suggests that chronic passive congestion with resulting anoxemia, by increasing the susceptibility of the hepatic tissue, is also a contributing factor to fibrosis in the portal areas.

By the evidence obtained in this investigation the meaning of the term "cardiac cirrhosis" is clarified. Cardiac cirrhosis signifying morphologic increase in connective tissue in the liver consequent to congestive failure is present in the majority of patients who have suffered from even mild congestive failure for nine months or more; the fibrosis may be central or portal or both. Clinical cardiac cirrhosis, signifying extreme fibrosis which clearly results from chronic passive congestion and which causes evidences of portal obstruction, does occur, but is rare. Of the 286 cases of congestive failure, there were only 15 in which marked but not necessarily predominant ascites required abdominal paracentesis. The clinical diagnosis of cardiac cirrhosis can be made only rarely, since it must be based on the finding of preponderant ascites, a small liver in spite of elevation of the venous pressure, and particularly the presence of a palpable spleen. Not infrequently, however, the liver may be enlarged. In such cases, although increased fibrous tissue is present and

the surface of the liver is generally nontender and sometimes somewhat irregular, the dilatation of the sinusoids leads to an increase in the size of the liver. In a patient in whose case a clinical diagnosis of cardiac cirrhosis has been made, one may find portal or central fibrosis, singly or in combination, or diffuse patchy fibrosis.

Dr. Henry A. Christian made it possible for us to use the records of the Peter Bent Brigham Hospital. Dr. Monroe J. Schlesinger cooperated in the study of the pathologic material.

HEMATOLOGY OF STERNAL MARROW AND VENOUS BLOOD OF PREGNANT AND OF NONPREGNANT WOMEN

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AND
EVELYN A. PACKHAM, R.N.
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The study of marrow obtained by sternal puncture has been in use at the Vancouver General Hospital since the appearance of the paper by Young and Osgood,[1] and the method has proved of great value. Recently, however, the problem of interpretation of the picture presented by the marrow of pregnant women was raised when marrow was obtained for study from a woman aged 24 years, four months pregnant, with acute lead poisoning. Search of the literature failed to reveal any figures for the sternal marrow of healthy pregnant women, and most of the figures available for healthy persons were based on studies of men only.

The studies herein reported were undertaken with the object of providing normal standards for these groups.

MATERIAL AND METHODS OF THE VANCOUVER GENERAL HOSPITAL

Subjects.—Forty pregnant women attending the outpatient maternity clinic of the Vancouver General Hospital were studied. None of these women had a past history suggesting a blood dyscrasia, and all of them were found by consideration of the history and by physical examination at the clinic to be in good health. For comparison, studies were made on 24 healthy nonpregnant women of about the same age. Nurses, technicians and others on the hospital staff volunteered for this purpose. All of those selected felt themselves to be perfectly well at the time of examination, and most of them were found to be healthy according to the history and the results of physical examination. The average age of the pregnant women was 24 years (range 17 to 34 years), and that of the nonpregnant women, 27 years (range 19 to 34 years).

Methods.—All methods used were those recommended by Osgood in his "Textbook of Laboratory Diagnosis" [2] and in the "Atlas of Hematology" by Osgood and Ashworth.[3]

From the Vancouver General Hospital.

1. Young, R. H., and Osgood, E. E.: Sternal Marrow Aspirated During Life: Cytology in Health and in Disease, Arch. Int. Med. **55**:186 (Feb.) 1935.

2. Osgood, E. E.: A Textbook of Laboratory Diagnosis, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1935.

3. Osgood, E. E., and Ashworth, C. M.: Atlas of Hematology, San Francisco, J. W. Stacey, Inc., 1937.

By sternal puncture (Osgood and Ashworth,[3] page 205) 10 cc. of marrow was obtained. This was introduced into a tube containing 2 mg. of oxalate (Osgood,[2] page 393) per cubic centimeter. Ten cubic centimeters of blood was obtained by venipuncture and introduced into oxalate. On each specimen of marrow, erythrocyte and total nucleated cell counts, hemoglobin estimation, a differential cell count of 500 cells in a smear stained with Wright's stain, a reticulocyte count and determination of the sedimentation rate were performed. On the blood the same procedures were used except that only 200 cells were counted in the differential counts. All of the laboratory studies were made by one of us (E. A. P.) with research care.

The erythrocyte, leukocyte and total nucleated cell counts were done in duplicate with pipets calibrated by the Bureau of Standards with meticulous attention to detail (Osgood,[2] page 404). The hemoglobin estimations were made by the Haskins-Sahli method (Osgood,[2] page 396). The results are reported both in grams and in percentage of the normal hemoglobin coefficient for women (Osgood,[2] page 420). The sedimentation rates were determined by the modified Westergren method (Osgood,[2] page 431) for use with oxalated blood. Reticulocyte counts were made by the Osgood and Wilhelm method (Osgood and Ashworth,[3] page 206). Before the differential counts were made the slides were surveyed under lower magnification (Osgood and Ashworth,[3] page 143) to select areas for counting where the erythrocytes did not touch each other and where the leukocytes were evenly distributed. If the counts from different slides did not check within reasonable limits, 300, and in rare instances 500, additional cells were counted on the marrow smears. The nomenclature and the criteria of cell identification and classification are those given in tabular form and illustrated in the "Atlas of Hematology" by Osgood and Ashworth.[3]

RESULTS

The results of these studies are given in tables 1 to 11.

Limitation of space makes it necessary to exclude from the tables such cells as proplasmacytes (Türk cells), plasmacytes, basophilic granulocytes (myelocytes) and eosinophilic and basophilic progranulocytes (promyelocytes), which were all present in numbers less than 0.1 per cent. For reasons of economy, also, eosinophilic metagranulocytes (metamyelocytes) were included with the eosinophilic granulocytes and the mature eosinophils with the eosinophilic rhabdocytes (staff cells).

COMMENT

It should be noted (tables 2 and 6), as Dieckmann and Wegner [4] have shown, that the erythrocyte counts and hemoglobin estimations for pregnant women are 10 to 15 per cent lower than for healthy nonpregnant women of the same age group. The erythrocyte and hemoglobin values for healthy nonpregnant women (tables 4 and 6) are somewhat lower than those reported by others [5] for healthy women of this age group, but the series investigated was small. The hemoglobin and

4. Dieckmann, W. J., and Wegner, C. R.: The Blood in Normal Pregnancy: I. Blood and Plasma Volumes, Arch. Int. Med. **53**:71 (Jan.) 1934; Studies of the Blood in Normal Pregnancy: II. Hemoglobin, Hematocrit and Erythrocyte Determinations and Total Amount of Variations of Each, ibid. **53**:188 (Feb.) 1934.

5. Osgood, E. E.: Normal Hematologic Standards, Arch. Int. Med. **56**:849 (Nov.) 1935.

TABLE 1.—*Values for Sternal Marrow of Healthy Pregnant Women*

TABLE I.—*Values for Sternal Marrow of Healthy Pregnant Women*

	Case Number	Age	Erythrocytes per Cu. Mm.	Color Index	Hemoglobin, %	Hemoglobin, Gm.	Sedimentation, 15 and 45 Minute Readings	Reticulocytes, %	Total Nucleated Cell Count per Cu. Mm.	Granuloblasts, % (Myeloblasts)	Progranulocytes Type A, % (Promyelocytes Type A)	Progranulocytes Type S, % (Promyelocytes Type S)	Eosinophilic Granulocytes, % (Eosinophilic Myelocytes)	Neutrophilic Granulocytes,% (Neutrophilic Myelocytes)	Metagranuloeytes, % (Metamyelocytes)	Rhabdocytes, % (Unsegmented Polymorphonuclears)	Lobocytes, % (Segmented Polymorphonuclears)	Eosinophils, %	Basophils, %	Lymphocytes, %	Monocytes, %	Megaloblasts: Karyoblasts, %	Megaloblasts: Prokaryocytes, %	Normoblasts: Karyocytes, %	Normoblasts: Metakaryocytes, %	Disintegrated Cells, %
Trimester 1	1	32	3,150,000	1.06	67	9.58	0/2	2.5	45,000	0.2	2.0	1.5	0.5	7.0	5.0	33.0	9.0	0.5	0	14.0	1.0	0.2	2.0	2.0	6.0	18.0
	2	17	3,100,000	1.02	62	8.87	3/20	2.0	40,000	0.2	0.6	1.0	1.0	4.0	5.0	46.0	10.5	1.0	0	11.0	0.1	0.2	2.1	1.6	2.7	13.5
	3	20	3,960,000	0.97	76	10.90	3/24	3.0	65,700	0.5	1.3	1.0	0.3	6.6	9.0	43.0	12.0	1.0	0	4.5	0.5	0.2	2.0	4.0	1.8	12.0
	4	23	4,100,000	0.90	74	10.63	3/11	1.3	19,000	0.2	0.2	0.6	2.6	4.4	6.0	19.0	22.0	6.0	1.0	15.6	3.0	0.2	3.2	4.6	1.4	10.6
	5	20	3,480,000	1.01	70	10.07	1/2	5.0	37,100	0	1.0	0.2	0.4	10.6	7.6	31.2	12.2	0.4	0.4	7.8	2.6	0	3.2	5.0	2.6	14.8
	6	22	3,560,000	1.08	77	11.04	5/25	4.0	46,500	0.2	0.6	0.4	0.6	7.4	5.4	33.0	19.0	1.0	0	12.2	0.4	0	2.0	4.2	3.0	10.2
	7	28	3,570,000	1.07	76	10.90	0/1	2.5	24,000	0	0.4	0.6	0.4	6.0	4.6	34.0	17.8	0.2	0.6	13.2	1.0	0.2	0.8	3.8	1.2	15.4
	8	34	4,250,000	0.96	82	11.73	1/7	2.8	19,700	0	0.4	0	0.2	3.4	4.6	18.0	33.6	1.4	1.0	17.8	1.0	0.2	2.4	2.4	1.0	11.6
	9	23	3,800,000	1.01	77	11.04	0/1	2.8	34,400	0	2.1	1.0	0.8	9.0	8.0	30.0	12.0	0.6	0.2	11.2	0.6	0.4	2.8	2.6	1.8	17.0
	10	24	3,860,000	1.03	80	11.50	0/1	2.3	14,400	0	1.4	0.2	0.2	1.2	1.8	15.2	37.6	1.0	0.2	28.0	1.0	0	0.6	1.8	0.2	9.6
Trimester 2	1	17	3,350,000	1.06	71	10.22	3/25	1.4	50,000	0.5	0.7	0.5	0.2	4.0	4.0	43.5	10.0	0.2	...	11.0	1.0	0.2	1.0	3.0	4.0	16.0
	2	19	3,360,000	1.01	67	9.58	1/2	2.0	17,500	0.1	1.0	0.9	0.1	5.0	4.0	34.0	9.0	0.1	0.1	17.0	0.1	1.0	4.0	6.4	7.0	10.7
	3	24	(——— Material not sufficient ———)							0.8	1.0	1.0	0	8.0	4.0	34.4	20.5	1.0	0.1	15.5	0.1	0	2.0	2.0	0.4	9.4
	4	20	4,410,000	1.05	93	13.50	1/2	0.7	25,000	0	0.6	0.8	0.2	7.2	7.8	20.6	20.2	0.6	0.2	15.6	1.0	0.2	2.0	2.2	1.0	17.6
	5	28	3,850,000	1.00	77	11.04	4/12	2.0	17,200	0.4	0.4	0.8	0.6	5.8	6.2	24.0	18.2	1.2	0.4	9.8	1.0	0	2.6	3.6	2.0	23.0
	6	33	3,610,000	1.11	80	11.45	3/15	2.7	125,000	1.0	2.0	2.8	1.0	10.5	8.2	37.0	9.4	0.3	0.1	8.0	0.2	0	1.5	5.6	1.2	9.2
	7	23	3,610,000	1.00	72	10.30	0/3	2.2	21,600	0.4	0.4	0.4	0.2	6.6	4.2	38.6	15.2	1.8	0.4	18.2	0.2	0.2	1.2	5.6	1.6	4.8
	8	27	3,890,000	1.02	80	11.45	4/19	1.4	15,700	0	1.4	0.6	0.2	4.2	1.6	19.6	19.8	1.8	0.6	25.0	1.8	0.2	1.6	2.0	1.2	18.4
	9	22	4,370,000	0.91	79	11.32	2/12	1.7	40,100	0.2	0.6	0	0.4	5.4	3.8	42.0	21.6	1.4	0	8.6	1.6	0.2	1.2	2.2	1.6	9.0
	10	21	3,750,000	1.00	74	10.97	3/34	1.0	30,750	0.4	1.4	0.4	0.4	7.8	4.4	30.8	18.6	0.6	0.2	11.0	0.6	0	2.2	3.8	1.8	15.4
	11	23	3,800,000	1.07	82	11.73	2/22	4.0	48,200	0.8	1.4	0.8	0.2	8.8	5.2	38.4	12.6	0.6	...	5.6	1.0	0	2.8	5.4	2.0	14.4
	12	17	3,230,000	0.89	57	8.14	2/10	2.6	33,900	0	0.6	0.6	0	11.2	7.6	36.0	11.0	0.8	0.2	11.8	...	0.6	2.2	4.2	2.4	10.8
	13	18	3,400,000	1.05	72	10.55	4/33	2.6	36,000	0.2	0.4	0.4	0.2	6.0	5.6	30.2	20.4	0.6	0	12.0	0.6	0.2	3.2	5.0	2.6	11.6
	14	25	3,260,000	1.12	73	10.44	0/1	4.0	30,300	0	1.0	0.2	0	6.0	6.2	34.4	15.0	0.4	0	16.6	0.4	0	1.4	4.8	2.8	10.8
	15	21	3,260,000	1.03	67	9.52	8/41	5.6	90,000	0.1	1.0	1.0	1.6	8.6	8.6	47.6	8.0	1.1	0.1	8.6	0.3	0.2	2.0	4.0	1.2	6.0
Trimester 3	1	19	3,200,000	1.09	70	10.01	4/20	0	70,000	0.1	1.0	1.0	1.0	9.0	7.0	42.0	6.0	1.0	0.1	7.0	0.1	0.1	3.0	2.0	3.0	17.0
	2	25	3,470,000	0.87	60	8.58	6/39	1.0	17,000	0	0.7	0.3	0.3	2.3	2.0	31.0	25.0	1.0	0.3	23.3	0.7	0	0.3	0.3	0.7	11.3
	3	23	3,600,000	1.00	72	10.30	1/2	3.0	42,000	0.1	2.0	2.5	0.1	4.0	4.5	38.0	13.0	0.1	0	5.5	0.5	0.5	3.0	3.0	6.5	17.0
	4	19	4,000,000	0.98	79	11.30	2/15	3.0	34,000	0.2	0	1.0	0.1	3.0	6.0	44.5	17.5	0.1	0	15.0	0.1	0.1	2.0	2.5	3.0	5.5
	5	26	3,300,000	1.06	70	10.01	1/45	1.0	22,600	0.1	0.8	1.0	0.1	4.6	4.6	42.0	9.2	0.8	0	11.0	0.1	0	2.0	4.6	4.4	15.0
	6	25	3,300,000	0.95	63	9.01	12/56	2.2	21,100	0.1	0.9	1.0	0.1	3.4	3.4	44.0	20.9	0.5	0.1	10.5	0.7	0.5	2.4	3.4	2.1	6.3
	7	29	3,800,000	0.92	70	10.01	1/3	1.1	24,600	0	1.2	1.2	0	4.2	3.0	31.6	1.6	1.0	0.2	15.2	0.4	0.2	4.2	5.8	3.8	23.6
	8	23	4,100,000	0.95	78	11.18	0/2	1.0	45,000	0	0.5	0.5	0.5	3.0	4.0	39.5	18.0	0	0	12.0	0	0	2.0	6.0	2.0	11.0
	9	26	4,000,000	0.97	78	11.18	10/45	2.0	28,500	0.2	0.4	0.8	0.4	2.6	7.2	26.6	15.2	0.4	0	11.4	0.4	0	4.0	8.8	1.6	13.2
	10	26	3,550,000	1.05	75	10.73	12/48	1.8	20,400	0	0.8	0.4	0.8	4.4	5.6	24.2	14.6	1.6	0.6	17.0	2.0	0	2.0	8.0	1.6	16.4
	11	33	3,430,000	0.91	62	8.83	2/6	1.5	34,000	0.4	0.4	1.0	0.6	3.8	6.0	36.0	19.2	0.2	0	14.2	1.4	0.2	2.2	5.0	1.0	8.6
	12	27	3,700,000	1.00	74	10.49	1/7	1.5	43,400	0.2	1.0	0.4	0.2	5.0	5.4	31.6	20.0	0.6	0.2	10.6	0.4	0.4	3.0	3.4	0.6	13.0
	13	21	3,920,000	0.92	72	10.35	3/24	4.5	30,000	0.2	0.8	1.0	0.4	7.4	8.0	37.2	13.6	1.0	0	11.8	1.0	0.4	1.8	4.0	1.4	10.6
	14	27	4,370,000	0.77	67	9.52	5/32	1.7	16,900	0.2	1.0	0.8	0.4	2.4	2.0	29.0	6.6	0.2	0.1	7.8	0.4	0.1	3.8	7.6	3.0	20.4
	15	23	4,350,000	0.85	74	10.63	4/31	4.4	63,500	1.0	2.3	1.3	1.0	12.5	6.2	23.5	8.3	1.0	0.3	6.7	0.2	0.2	6.2	13.6	2.3	13.2
	16	29	4,000,000	1.05	84	12.01	3/16	3.0	30,500	1.0	0.6	2.0	0.6	6.0	3.8	31.4	19.6	1.4	0.6	13.0	2.0	0	3.6	4.0	1.2	8.4

TABLE 2.—*Values for Blood* of Healthy Pregnant Women*

	Case Number	Erythrocytes per Cu. Mm.	Color Index	Hemoglobin, %	Hemoglobin, Gm.	Sedimentation, 15 and 45 Minute Readings	Reticuloeytes, %	Leukocytes per Cu. Mm.	Polymorphonuclears, %	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils, %	Disintegrated Cells, %
Tri-mester 1	1	4,130,000	1.00	82	11.73	Not done		9,800		Normal range				
	2	3,000,000	1.02	64	9.15	Not done		9,600		Normal range				
	3	4,400,000	0.93	82	11.80	4/25	2.6	12,100	74	16	1	0	1	8
	4	4,280,000	0.92	76	10.72	2/11	2.4	8,500	57	31	1	5	0	6
	5	3,780,000	1.02	77	11.01	2/8	4.5	9,450	69	21	6	1	1	2
	6	3,710,000	1.04	77	11.04	8/38	2.0	14,500	57	34	0	4	0	5
	7	4,220,000	0.94	79	11.32	1/8	3.0	9,000	65	32	0	0	0	3
	8	4,550,000	9.96	87	12.42	1/8	2.6	12,250	78	16	2	2	0	2
	9	3,990,000	1.06	84	12.01	1/9	2.2	7,750	61	28	3	1	2	5
	10	3,920,000	1.05	82	11.73	1/6	2.0	9,950	66	26	2	1	0	5
Tri-mester 2	1	3,700,000	1.02	76	10.90	5/29	Not done	10,000	53	41	Normal range			
	2	3,250,000	1.06	69	9.80	4/16	Not done	9,050		Normal range				
	3													
	4	5,000,000	0.93	93	13.25	1/6	Not done	10,000	64	24	6	3	0	3
	5	4,230,000	0.94	77	11.04	6/31	Not done	8,100	71	12	7	3	0	7
	6	4,460,000	0.90	81	11.59	9/36	Not done	13,700	69	18	0	1	0	7
	7	3,850,000	0.96	73	10.44	2/26	1.8	7,200	67	20	4	5	0	4
	8	3,880,000	1.07	83	11.87	3/21	2.3	11,000	60	49	6	0	0	7
	9	4,350,000	0.90	78	11.18	2/18	1.6	12,050	78	13	1	1	2	4
	10	4,000,000	0.98	79	11.35	4/35	1.0	13,160	77	14	4	2	0	3
	11	4,140,000	1.04	86	12.30	5/33	2.2	11,200	74	19	4	0	1	2
	12	3,380,000	0.89	59	8.42	6/40	2.2	8,700	55	33	1	0	0	11
	13	3,750,000	1.01	76	10.90	7/36	2.0	10,500	78	15	5	0	0	1
	14	3,880,000	1.00	76	10.87	5/26	3.6	13,500	66	29	2	1	0	2
	15	3,720,000	0.93	69	9.80	10/52	4.0	12,850	67	29	1	0	0	5
Tri-mester 3	1	3,500,000	0.95	67	9.58	5/29				Not done				
	2	4,020,000	0.90	72	10.30	7/36	Not done	13,100		Normal range				
	3	3,500,000	1.00	70	10.01	5/25	Not done	6,350	72	Normal range				
	4	4,200,000	1.02	86	12.30	4/27	Not done	12,200	70	29	1	0	0	0
	5	3,450,000	0.97	67	9.58	13/59	Not done	6,800		Normal range				
	6	3,800,000	0.92	70	10.01	15/65	Not done	9,300		Normal range				
	7	3,640,000	0.97	70	10.01	10/34	Not done	7,600		Normal range				
	8	3,800,000	1.01	77	11.01	2/13	Not done	6,800		Normal range				
	9	3,850,000	1.01	78	11.18	12/52	Not done	7,000	65	26	3	3	0	3
	10	3,750,000	1.00	75	10.76	12/45	Not done	7,500	54	38	0	0	1	7
	11	3,310,000	0.94	63	8.97	5/26	Not done	8,950	64	28	2	0	0	6
	12	3,900,000	0.96	75	10.76	2/15	Not done	11,800	62	30	1	2	0	5
	13	4,180,000	0.91	75	10.76	10/40	Not done	7,400	43	48	3	1	1	4
	14	4,266,000	0.77	66	9 38	5/40	1.9	6,900	71	23	4	0	0	2
	15	4,500 000	0.83	75	10.76	2/40	3.4	9,600	78	11	3	1	0	7
	16	4,300,000	1.01	87	12.44	5/23	Not done	11,800	64	29	1	0	1	5

* Peripheral blood was used for the determinations.

TABLE 3.—*Values for Sternal Marrow of Healthy Nonpregnant Women*

Case Number	Age	Erythrocytes per Cu. Mm.	Color Index	Hemoglobin, %	Hemoglobin, Gm.	Sedimentation, 15 and 45 Minute Readings	Reticulocytes, %	Total Nucleated Cell Count per Cu. Mm.	Granuloblasts, % (Myeloblasts)	Progranulocytes Type A, % (Promyelocytes Type A)	Progranulocytes Type S, % (Promyelocytes Type S)	Eosinophilic Granulocytes, % (Eosinophilic Myelocytes)	Neutrophilic Granulocytes, % (Neutrophilic Myelocytes)	Metagranulocytes, % (Metamyelocytes)	Rhabdocytes, % (Unsegmented Polymorphonuclears)	Lobocytes, % (Segmented Polymorphonuclears)	Eosinophils, %	Basophils, %	Lymphocytes, %	Monocytes, %	Megaloblasts		Normoblasts		Disintegrated Cells, %
																					Karyoblasts, %	Prokaryocytes, %	Karyocytes, %	Metakaryocytes, %	
1	34	3,890,000	1.06	84	12.01	0/1	1.2	12,000	0	0.2	0.2	0.2	1.0	1.4	16.8	24.4	1.0	0.6	19.6	0	0	2.8	6.2	3.2	20.4
2	19	4,000,000	1.12	90	12.87	0/1	1.0	15,300	0	0.4	0.4	0	5.4	2.6	25.8	14.0	1.8	0.2	16.2	2.6	0	3.6	6.6	1.0	19.0
3	26	3,700,000	0.97	72	10.35	0/2	1.0	36,300	0.3	0.6	1.0	1.5	7.0	7.3	26.0	11.5	1.0	0.1	10.3	1.0	0	3.5	8.0	3.0	18.0
4	25	4,390,000	0.95	83	11.87	1/7	1.1	10,700	0.1	0.1	0.4	0.4	4.0	4.0	16.0	25.0	6.0	0.1	23.2	3.2	0.1	0.6	2.4	0.4	14.4
5	25	4,100,000	1.03	85	12.14	0/1	3.2	32,600	0.2	0.4	1.2	0.4	8.0	7.8	20.8	12.2	0.6	0	20.0	2.2	0	4.0	6.0	1.6	14.0
6	27	4,320,000	1.04	90	12.83	1/2	1.4	22,000	0.2	0.6	0	0.6	4.0	9.4	26.8	14.4	1.0	0.8	15.2	2.0	0.1	2.0	4.8	3.0	15.0
7	28	3,980,000	0.98	77	11.04	1/4	1.6	15,500	0.6	1.0	0.1	0	6.0	5.4	20.0	11.4	1.4	0.5	23.0	1.4	0.1	1.6	5.0	1.7	22.0
8	32	4,020,000	1.01	81	11.59	1/5	1.1	30,600	0.4	1.2	0.8	0.4	7.2	7.6	28.0	15.6	0.6	0.6	10.6	2.0	0.4	2.4	5.6	3.0	13.6
9	25	4,000,000	0.93	75	10.63	1/3	1.5	10,300	0.3	1.0	0.3	0.4	3.0	3.0	13.0	31.0	2.7	0.5	29.0	3.5	0	0.6	1.3	0.5	10.5
10	23	4,460,000	0.97	86	12.28	1/2	1.5	17,900	0.4	1.4	0.6	0.2	3.6	6.0	18.4	16.4	1.0	0.8	24.8	2.4	0.4	2.4	4.4	1.4	14.8
11	24	4,400,000	1.08	95	13.72	1/3	2.1	8,800	0.4	1.0	0.6	0	3.2	3.8	12.4	24.6	1.2	0.1	30.4	1.6	0	1.2	3.4	1.0	14.8
12	28	4,500,000	0.98	88	12.70	3/7	2.3	46,000	0.4	1.6	0.8	0.8	7.4	9.4	31.4	15.4	0.8	0.2	12.4	0.8	0	1.6	3.2	0.8	12.4
13	26	4,420,000	0.96	86	12.20	1/2	1.6	29,100	0.6	1.6	0.8	1.2	7.2	7.6	29.0	13.4	1.2	0.1	10.8	1.4	0	3.0	6.6	1.6	14.0
14	25	4,280,000	1.03	88	12.56	0/0	1.2	21,800	0.5	0.8	0.5	0.1	4.3	6.0	18.3	14.5	0.8	0	23.3	0.8	0	1.5	3.5	1.1	24.0
15	23	4,120,000	0.83	68	9.80	1/4	1.1	16,100	0	1.0	0	0.2	7.2	5.4	25.4	17.2	0.6	0.2	15.2	0.2	0	2.2	6.0	2.2	17.0
16	28	4,000,000	0.98	79	11.32	4/35	0.5	34,900	0.8	0.8	0.6	0.4	8.6	5.2	30.8	10.4	0.8	0.2	15.0	0.6	0.2	4.0	5.0	2.4	14.0
17	27	4,280,000	1.03	88	12.56	0/4	2.2	45,000	0.6	1.4	1.4	1.0	9.2	6.0	32.2	15.0	0.2	0	10.0	1.4	0.2	3.0	4.6	1.8	11.6
18	28	4,250,000	1.03	88	12.56	1/2	2.4	26,500	0.6	1.4	0.2	0.8	9.0	5.0	24.6	11.8	2.2	0	15.2	1.0	0	4.0	5.6	3.2	15.2
19	31	3,800,000	1.09	83	11.87	1/6	1.6	34,600	0.2	1.0	0.6	1.0	6.6	5.4	34.2	18.2	1.0	0	9.4	1.2	0.2	2.8	5.0	1.4	11.8
20	31	4,300,000	0.95	82	11.73	0/1	2.2	7,550	0.2	1.0	0	0.4	4.4	5.0	15.4	15.0	0.8	0.2	22.8	1.4	0	2.8	6.0	1.4	23.2
21	23	4,300,000	0.94	81	11.59	1/2	2.4	15,700	0.4	1.4	0.8	1.0	4.6	5.0	22.2	17.6	0.6	0	13.6	1.2	0.4	3.6	8.0	3.0	16.4
22	30	4,350,000	1.04	90	12.83	0/1	3.0	27,800	0.4	1.2	0	0.2	11.0	7.0	30.2	12.4	0.2	0.6	9.2	0.8	0.4	2.6	5.8	2.6	15.4
23	33	4,030,000	1.02	82	11.73	0/4	2.8	25,000	0	2.2	0.8	0.8	6.0	4.2	29.0	19.4	1.2	0	8.6	1.0	0	1.4	4.0	1.4	19.6
24	31	4,280,000	0.91	77	11.04	1/8	3.8	14,900	0.8	1.0	0.4	0.6	5.4	5.2	21.0	18.4	2.2	0.6	16.8	1.4	0.2	2.2	4.4	2.6	16.8

akaryocyte (non-nucleated erythrocyte) counts for the marrow in pregnancy (tables 1 and 5) are somewhat lower than the corresponding counts for the blood (tables 2 and 6). The leukocyte counts of the blood during pregnancy (tables 2 and 6) are significantly higher than

TABLE 4.—*Values for Blood* of Healthy Nonpregnant Women*

Case Number	Erythrocytes per Cu. Mm.	Color Index	Hemoglobin, %	Hemoglobin, Gm.	Sedimentation, 15 and 45 Minute Readings	Reticulocytes, %	Leukocytes per Cu. Mm.	Polymorphonuclears, %	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils, %	Disintegrated Cells, %
1.....	4,010,000	1.06	85	12.16	1/4	Not done	6,800	53	40	1	1	0	5
2.....	4,300,000	1.09	94	13.44	1/30	Not done	5,500	40	50	5	0	0	5
3.....	3,900,000	0.98	77	11.04	2/12	Not done	6,000	46	43	6	1	1	3
4.....	4,500,000	0.95	86	12.28	1/9	Not done	8,600	60	30	3	2	0	5
5.....	4,420,000	0.95	84	12.01	1/2	Not done	9,500	40	49	5	2	0	4
6.....	4,570,000	1.00	91	12.97	1/4	Not done	8,600	59	26	5	6	1	3
7.....	4,020,000	0.97	78	11.18	1/8	Not done	8,300	38	48	8	1	1	4
8.....	4,220,000	0.98	83	11.87	0/8	Not done	6,000	47	45	3	0	1	4
9.....	4,100,000	0.92	76	10.90	1/3	Not done	10,300	54	32	3	2	1	7
10.....	4,750,000	0.92	87	12.42	1/2	Not done	7,300	52	34	5	2	1	6
11.....	4,550,000	1.08	99	14.27	0/2	Not done	5,200	52	42	3	1	1	2
12.....	4,300,000	1.00	86	12.44	3/11	Not done	9,000	72	19	3	1	1	4
13.....	4,540,000	0.96	87	12.35	2/8	Not done	5,000	44	46	3	5	0	2
14.....	4,510,000	0.98	89	12.70	0/2	1.2	7,700	41	46	2	2	0	8
15.....	4,200,000	0.85	72	10.35	2/20	0.9	6,600	60	27	6	0	1	6
16.....	4,100,000	0.92	76	10.90	6/38	0.5	12,500	63	21	5	1	1	9
17.....	4,460,000	1.02	90	12.82	1/5	1.7	6,250	55	33	6	2	0	4
18.....	4,350,000	1.03	90	12.83	1/3	2.0	6,250	47	40	3	5	0	5
19.....	4,380,000	0.98	85	12.14	1/10	1.5	10,500	45	45	3	1	1	5
20.....	4,330,000	0.96	83	11.87	1/10	1.8	5,350	52	36	3	0	2	7
21.....	4,880,000	0.92	89	12.70	1/6	1.0	9,750	57	38	5	0	0	0
22.....	4,690,000	1.02	95	13.52	1/2	2.0	5,800	46	41	7	3	0	3
23.....	4,560,000	0.97	89	12.70	0/4	2.5	10,050	76	16	2	2	0	4
24.....	4,790,000	0.92	87	12.42	0/4	3.0	5,700	51	41	2	0	0	6

* Peripheral blood was used for the determinations.

for healthy nonpregnant women (tables 4 and 6). The leukocyte counts of the blood of healthy nonpregnant women (tables 4 and 6) agree well with those reported by Osgood for a larger group.[6] The total nucleated cell counts for the marrow are definitely higher in pregnant (tables 1 and 5) than in nonpregnant women (tables 3 and 5), and the averages and ranges for healthy nonpregnant women (tables 5 and 10) agree well with those reported by Young and Osgood[1] for healthy

6. Osgood, E. E.: Total, Differential and Absolute Leukocyte Counts and Sedimentation Rate in Adults, to be published.

TABLE 5.—*Comparison of Average, Maximum and Minimum Values for Sternal Marrow in the Three Trimesters of Pregnancy and for Pregnant and Nonpregnant Women*

	Age	Erythrocytes per Cu. Mm.	Color Index	Hemoglobin, %	Hemoglobin, Gm.	Sedimentation (Modified Westergren) 15 and 45 Minute Readings	Reticulocytes, %	Total Nucleated Cell Count per Cu. Mm.	Granuloblasts, % (Myeloblasts)	Progranulocytes Type A, % (Promyelocytes Type A)	Progranulocytes Type S, % (Promyelocytes Type S)	Eosinophilic Granulocytes, % (Eosinophilic Myelocytes)	Neutrophilic Granulocytes, % (Neutrophilic Myelocytes)	Metagranulocytes, % (Metamyelocytes)	Rhabdocytes, % (Unsegmented Polymorphonuclears)	Lobocytes, % (Segmented Polymorphonucleers)	Eosinophils, %	Basophils, %	Lymphocytes, %	Monocytes, %	Megaloblasts		Normoblasts		Disintegrated Cells, %
																					Karyoblasts, %	Prokaryocytes, %	Karyocytes, %	Metakaryocytes, %	
Trimester 1:																									
Maximum....	34	4,250,000	1.08	82	11.73	5/25	5.0	65,700	0.5	2.1	1.5	2.6	10.6	9.0	46.0	37.6	6.0	1.0	28.0	3.0	0.4	3.2	5.0	6.0	18.0
Minimum....	17	3,100,000	0.90	62	8.87	0/1	1.3	14,400	0.0	0.2	0.0	0.2	1.2	1.8	15.2	9.0	0.2	0.0	4.5	0.1	0.0	0.6	1.6	0.2	9.6
Average.....	24	3,680,000	1.01	74	10.62	2/9	2.8	34,580	0.1	1.0	0.7	0.7	6.0	5.7	30.2	18.6	1.3	0.3	13.5	1.1	0.2	2.1	3.2	2.2	13.3
Trimester 2:																									
Maximum....	33	4,410,000	1.12	93	13.50	8/41	5.6	125,000	1.0	2.0	2.8	1.6	11.2	8.6	47.6	21.6	1.8	0.6	25.0	1.8	1.0	4.0	6.4	7.0	23.5
Minimum....	17	3,230,000	0.89	57	8.14	0/1	1.7	15,700	0.0	0.4	0.0	0.0	4.0	1.6	19.6	8.0	0.1	0.0	5.6	0.0	0.0	1.0	2.0	0.4	6.0
Average.....	23	3,650,000	1.02	75	10.04	3/17	2.4	41,510	0.3	0.9	0.7	0.4	7.0	5.4	34.0	15.3	0.8	0.1	12.9	0.7	0.2	2.0	4.0	2.2	12.4
Trimester 3:																									
Maximum....	33	4,370,000	1.09	84	12.01	12/56	4.5	70,000	1.0	2.3	2.5	1.0	12.5	9.0	44.5	25.0	1.6	0.6	23.3	2.4	0.5	6.2	13.6	6.5	23.6
Minimum....	19	3,200,000	0.77	60	8.58	0/2	1.0	16,900	0.0	0.0	0.3	0.0	2.3	2.0	23.5	1.6	0.0	0.0	5.5	0.0	0.0	0.3	0.3	0.6	5.5
Average.....	25	3,750,000	0.96	72	10.25	4/24	2.2	33,900	0.2	0.9	1.0	0.4	5.7	5.3	34.5	14.3	0.7	0.2	12.9	0.7	0.2	2.8	5.3	2.4	13.2
Pregnant women:																									
Maximum....	34	4,410,000	1.12	93	13.50	12/56	5.6	125,000	1.0	2.3	2.8	2.6	12.5	9.0	47.6	37.6	6.0	1.0	28.0	3.0	1.0	6.2	13.6	7.0	23.6
Minimum....	17	3,100,000	0.77	57	8.58	0/1	0.7	14,400	0.0	0.0	0.0	0.0	1.2	1.6	15.2	1.6	0.0	0.0	4.5	0.0	0.0	0.3	0.3	0.2	5.5
Average.....	24	3,700,000	0.99	73	10.27	3/18	2.4	36,760	0.2	0.9	0.8	0.5	6.3	5.5	33.3	15.7	0.9	0.2	12.7	0.8	0.2	2.4	4.3	2.3	12.9
Nonpregnant women:																									
Maximum....	34	4,500,000	1.12	95	13.52	4/35	3.8	46,000	0.8	2.2	1.4	1.5	11.0	9.4	34.2	31.0	6.0	0.8	30.4	3.5	0.4	4.0	8.0	3.2	24.0
Minimum....	19	3,700,000	0.83	68	9.80	0/0	0.5	7,550	0.0	0.1	0.0	0.0	1.4	1.4	12.4	10.4	0.2	0.0	9.2	0.0	0.0	0.6	1.3	0.4	10.5
Average.....	27	4,170,000	0.99	83	11.90	1/4	1.4	23,100	0.3	1.0	0.5	0.5	6.0	5.6	23.7	16.6	1.3	0.3	16.8	1.4	0.1	2.5	5.0	1.9	16.2

men. It is noteworthy that there is no decrease in any of the nucleated erythrocytes during pregnancy (tables 5 and 10), which indicates that the physiologic anemia of pregnancy is due not to decreased erythrocyte production but, as others have shown,[4] to the increase in plasma volume. There is even a slight increase in the reticulocyte counts during pregnancy (tables 2 and 6), suggesting that there may be a slightly increased rate of erythrocyte formation. The reticulocyte counts of the blood of healthy nonpregnant women (tables 4 and 6) agree well with those

TABLE 6.—*Comparison of the Average, Maximum and Minimum Values for Blood* in the Three Trimesters of Pregnancy and for Pregnant and Nonpregnant Women*

		Erythrocytes per Cu. Mm.	Color Index	Hemoglobin, %	Hemoglobin, Gm.	Sedimentation, 15 and 45 Minute Readings	Reticulocytes, %	Leukocytes per Cu. Mm.	Polymorphonuclears, %	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils, %	Disintegrated Cells, %
Trimester 1:														
Maximum	34	4,550,000	1.06	87	12.42	8/38	4.5	14,500	78	34	6	5	2	8
Minimum	17	3,000,000	0.92	64	9.15	1/6	2.0	7,750	57	16	0	0	0	2
Average	24	3,998,000	1.00	79	11.29	2/14	2.4	10,290	66	26	2	2	1	5
Trimester 2:														
Maximum	33	5,000,000	1.07	93	13.25	10/52	4.0	13,700	78	49	7	5	2	11
Minimum	17	3,250,000	0.89	59	8.42	1/6	1.0	7,200	53	12	0	0	0	1
Average	23	3,970,000	0.97	77	10.98	5/29	2.3	10,800	68	24	3	1	0.5	5
Trimester 3:														
Maximum	33	4,500,000	1.02	87	12.44	15/65	...	13,100	78	48	4	3	1	7
Minimum	19	3,310,000	0.77	63	8.97	2/13	...	6,350	43	11	0	0	0	0
Average	25	3,870,000	0.94	73	10.48	7/36	...	8,800	64	29	2	1	0.3	4
Pregnant women:														
Maximum	34	5,000,000	1.07	93	13.25	16/65	4.5	14,500	78	49	7	5	2	11
Minimum	17	3,000,000	0.77	59	8.42	1/6	1.0	6,300	43	11	0	0	0	0
Average	24	3,980,000	0.96	76	10.86	5/29	2.5	9,920	66	26	3	1	0.3	5
Nonpregnant women:														
Maximum	34	4,880,000	1.09	90	14.27	6/38	3.0	12,500	76	50	8	6	2	9
Minimum	19	3,900,000	0.85	72	10.35	0/2	0.5	5,000	38	16	1	0	0	0
Average	27	4,390,000	0.97	86	12.26	1/8	1.6	7,000	52	37	4	2	0.5	5

* Peripheral blood was used for the determinations.

reported by Osgood and Wilhelm[7] for a larger series. It is evident from the differential (tables 1 and 5) and absolute (tables 7 and 9) counts that the sternal marrow of pregnant women is somewhat hyperplastic as compared to the sternal marrow of healthy nonpregnant women (tables 8 and 9) but that the hyperplasia affects all types of cells about equally, so that the differential counts (tables 5 and 10) are not significantly different from those for healthy nonpregnant women. The

7. Osgood, E. E., and Wilhelm, M. M.: Reticulocytes, J. Lab. & Clin. Med. **19**:1129, 1934.

TABLE 7.—*Absolute Numbers of Each Type of Cell per Cubic Millimeter in Sternal Marrow of Pregnant Women*

TABLE 7.—*Absolute Numbers of Each Type of Cell per Cubic Millimeter in Sternal Marrow of Pregnant Women*

	Case Number	Total Nucleated Cell Count per Cu. Mm.	Granuloblasts (Myeloblasts)	Progranulocytes Type A (Promyelocytes Type A)	Progranulocytes Type S (Promyelocytes Type S)	Eosinophilic Granulocytes (Eosinophilic Myelocytes)	Neutrophilic Granulocytes (Neutrophilic Myelocytes)	Metagranulocytes (Metamyelocytes)	Rhabdocytes (Unsegmented Polymorphonuclears)	Lobocytes (Segmented Polymorphonuclears)	Eosinophils	Basophils	Lymphocytes	Monocytes	Megaloblasts: Karyoblasts	Megaloblasts: Prokaryocytes	Normoblasts: Karyocytes	Normoblasts: Metakaryocytes	Disintegrated Cells
Trimester 1	1	45,000	90	900	675	225	3,150	2,250	14,850	4,050	225	0	6,300	450	90	900	900	2,700	8,100
	2	40,400	80	240	400	400	1,600	2,000	18,400	4,200	400	0	4,400	40	80	840	640	1,800	5,400
	3	65,700	328	854	657	197	4,336	5,913	28,251	7,884	657	0	2,956	328	130	1,314	2,628	1,182	7,884
	4	19,000	38	38	114	494	836	1,140	3,610	4,180	1,140	190	2,964	570	38	608	874	266	2,014
	5	37,100	0	371	74	148	3,932	2,819	11,575	4,526	148	148	2,894	965	0	1,187	1,855	965	5,490
	6	46,500	93	279	186	279	3,441	2,511	15,345	8,835	465	0	5,673	186	0	930	1,953	1,395	4,743
	7	24,000	0	96	144	96	1,440	1,104	8,160	4,272	48	144	3,168	240	48	192	912	288	3,696
	8	19,700	0	78	0	39	669	906	3,546	6,619	275	197	3,506	197	39	472	472	197	2,285
	9	34,400	0	722	344	275	3,096	2,752	10,664	4,472	206	68	3,852	206	136	963	894	619	5,848
	10	14,400	0	202	28	28	172	259	2,189	5,414	144	28	4,032	144	0	86	259	28	1,382
Trimester 2	1	50,000	250	375	250	125	2,000	2,000	21,750	5,000	125	0	5,500	500	125	500	1,500	2,000	8,000
	2	17,500	18	175	157	18	875	700	5,950	1,575	18	18	2,975	18	175	700	1,120	1,225	1,872
	3	25,000	0	150	200	50	1,800	1,950	5,150	5,050	150	50	3,900	250	50	500	550	250	4,100
	4	17,200	69	69	138	103	998	1,066	4,128	3,130	206	69	1,686	172	0	447	619	344	3,956
	5	125,000	1,250	2,500	3,500	1,250	13,125	10,250	46,250	11,750	375	125	10,000	250	0	1,875	7,000	1,500	11,500
	6	21,600	86	86	86	43	1,426	907	8,338	3,283	389	86	3,931	43	43	259	1,210	346	1,037
	7	15,700	0	220	94	31	659	251	3,077	3,109	283	94	3,925	283	94	251	314	188	2,889
	8	40,100	80	241	0	160	2,165	1,524	16,842	8,662	561	0	3,449	642	80	481	882	642	3,609
	9	30,750	123	430	123	123	2,399	1,353	9,471	5,719	185	61	3,383	185	0	677	1,168	554	4,735
	10	48,200	386	675	386	96	4,242	2,506	18,509	6,073	289	0	2,699	482	0	1,350	2,603	964	6,941
	11	33,000	0	203	203	0	3,797	2,576	12,204	3,729	271	68	4,000	0	203	746	1,424	814	3,661
	12	36,000	72	144	144	72	2,160	2,016	10,872	7,344	216	0	4,320	216	72	1,152	1,800	936	4,176
	13	30,300	0	303	61	0	1,818	1,879	10,423	4,545	121	0	5,030	121	0	424	1,454	849	3,272
	14	90,000	90	900	900	1,440	7,740	7,740	42,840	7,200	990	90	7,740	270	180	1,800	3,600	1,080	5,400
Trimester 3	1	70,000	70	700	700	700	6,300	4,900	29,400	4,200	700	70	4,900	70	70	2,100	1,400	2,100	11,900
	2	17,000	0	119	51	51	391	340	5 270	4,250	170	51	3,961	119	0	51	51	119	1,921
	3	42,000	42	840	1,050	42	1,680	1,890	15,960	5,460	42	0	2,310	210	210	1,260	1,260	2,730	7,140
	4	34,000	68	0	340	34	1,020	2,040	15,130	5,950	34	0	5,100	34	34	680	850	1,020	1,870
	5	22,600	23	181	226	22	1,040	1,040	9,492	2,079	180	0	2,486	22	0	452	1,040	994	3,390
	6	21,100	21	190	211	21	717	717	9,284	4,410	105	21	2,216	148	105	506	717	443	1,329
	7	24,600	0	295	295	0	1,033	738	7,774	394	246	49	3,788	98	49	1,033	2,165	935	5,806
	8	45,000	0	225	225	225	1,350	1,800	17,775	8,100	0	0	5,400	0	0	900	2,700	900	4,950
	9	28,500	57	114	228	114	2,736	2,052	7,581	4,332	114	0	3,249	114	0	1,140	2,508	456	3,762
	10	20,400	0	163	82	163	899	1,142	4,937	2,978	326	122	3,468	408	0	408	1,632	326	3,346
	11	34,000	136	136	340	204	1,292	2,040	12,240	6,528	68	0	4,828	476	68	748	1,700	340	3,924
	12	43,400	87	434	174	87	2,170	2,343	13,714	8,680	260	87	4,600	174	174	1,302	1,476	260	5,642
	13	30,000	60	240	300	120	2,220	2,400	11,160	4,080	300	0	3,540	300	120	540	1,200	420	3,180
	14	16,900	34	169	135	68	1,589	1,521	4,901	1,115	34	17	1,318	68	17	642	1,284	507	3,448
	15	63.500	635	1,460	826	635	7,937	8.937	14.923	5,270	635	191	4,381	127	127	3.937	8.636	1,460	8,382
	16	30.500	305	183	610	183	1,830	1,159	9,577	5,978	427	183	3,965	732	0	1,098	1,220	366	2,684

TABLE 8.—*Absolute Numbers of Each Type of Cell per Cubic Millimeter in Sternal Marrow of Nonpregnant Women*

Case Number	Total Nucleated Cell Count per Cu. Mm.	Granuloblasts (Myeloblasts)	Progranulocytes Type A (Promyelocytes Type A)	Progranulocytes Type S (Promyelocytes Type S)	Eosinophilic Granulocytes (Eosinophilic Myelocytes)	Neutrophilic Granulocytes (Neutrophilic Myelocytes)	Metagranulocytes (Metamyelocytes)	Rhabdocytes (Unsegmented Polymorphonucleears)	Lobocytes (Segmented Polymorphonucleurs)	Eosinophils	Basophils	Lymphocytes	Monocytes	Megaloblasts: Karyoblasts	Megaloblasts: Prokaryocytes	Normoblasts: Karyocytes	Normoblasts: Metakaryocytes	Disintegrated Cells
1	12,000	0	24	24	24	168	168	2,016	2,928	120	72	2,352	0	0	336	744	384	2,448
2	15,300	0	61	61	0	826	398	3,947	2,142	275	31	2,479	398	0	551	1,010	153	2,907
3	36,300	109	218	363	544	2,541	2,650	9,438	4,174	363	36	3,739	363	0	1,270	2,904	1,089	6,534
4	10,700	11	11	43	43	428	428	1,712	2,675	642	10	2,484	342	10	64	257	43	1,541
5	32,600	65	130	391	130	2,608	2,543	6,781	3,977	196	0	6,520	717	0	1,304	1,956	522	4,564
6	22,000	44	132	0	132	880	2,068	5,896	3,168	220	176	3,344	440	22	440	1,056	660	3,300
7	15,500	93	155	16	0	930	847	3,100	1,767	217	77	3,565	217	16	248	775	264	3,410
8	30,600	122	367	245	122	2,203	2,326	8,568	4,774	184	184	3,244	612	122	734	1,714	918	4,162
9	10,300	31	103	31	41	309	309	1,339	3,193	278	51	2,987	360	0	62	134	51	1,081
10	17,900	72	251	107	36	644	1,074	3,294	2,936	179	143	4,439	430	72	430	788	251	2,649
11	8,800	35	88	53	0	282	334	1,091	2,165	106	9	2,675	141	0	106	299	88	1,302
12	46,000	184	736	368	368	3,404	4,324	14,444	7,084	368	92	5,704	368	0	736	1,472	368	5,704
13	29,100	175	466	233	349	2,095	2,212	8,439	3,899	349	29	3,143	407	0	873	1,921	466	4,074
14	21,800	109	174	109	22	937	1,308	3,989	3,161	174	0	5,079	174	0	327	763	240	5,232
15	16,100	0	161	0	32	1,159	869	4,089	2,769	97	32	2,447	32	0	354	966	354	2,737
16	34,900	279	279	209	140	3,001	1,815	10,749	3,630	279	70	5,235	209	70	1,396	1,745	838	4,886
17	45,000	270	630	630	450	4,140	2,700	14,490	6,750	90	0	4,500	630	90	1,350	2,070	810	5,220
18	26,500	159	371	53	212	2,385	1,325	6,519	3,127	583	0	4,028	265	0	1,060	1,484	848	4,028
19	34,600	69	346	208	346	2,284	1,868	11,833	6,297	346	0	3,252	415	69	969	1,730	484	4,083
20	7,550	15	76	0	30	332	377	1,163	1,132	60	15	1,721	106	0	211	453	106	1,752
21	15,700	63	220	126	157	722	785	3,485	2,763	94	0	2,135	188	63	565	1,256	471	2,575
22	27,800	111	334	0	56	3,058	1,946	8,396	3,447	56	167	2,558	222	111	723	1,612	723	4,281
23	25,000	0	550	200	200	1,500	1,050	7,250	4,850	300	0	2,150	250	0	350	1,000	350	4,900
24	14,900	119	149	60	89	805	775	3,129	2,742	328	89	2,503	209	30	328	656	387	2,503

TABLE 9.—*Comparison of Absolute Counts per Cubic Millimeter in Sternal Marrow During the Three Trimesters of Pregnancy and for Pregnant and Nonpregnant Women*

	Total Nucleated Cell Count per Cu. Mm.	Granuloblasts (Myeloblasts)	Progranulocytes Type A (Promyelocytes Type A)	Progranulocytes Type S (Promyelocytes Type S)	Eosinophilic Granulocytes, (Eosinophilic Myelocytes)	Neutrophilic Granulocytes (Neutrophilic Myelocytes)	Metagranulocytes (Meta-myelocytes)	Rhabdocytes (Unsegmented Polymorphonuclears)	Lobocytes (Segmented Polymorphonuclears)	Eosinophils	Basophils	Lymphocytes	Monocytes	Megaloblasts		Normoblasts		Disintegrated Cells
														Karyoblasts	Prokaryocytes	Karyocytes	Metakaryocytes	
Trimester 1:																		
Maximum	65,700	328	900	675	494	4,336	5,913	28,251	8,835	1,140	197	6,300	965	136	1,314	2,628	2,700	8,100
Minimum	14,400	0	38	0	28	172	259	2,189	4,050	48	0	2,894	40	0	86	259	28	1,382
Average	34,580	63	378	262	218	2,267	2,165	11,659	5,445	371	78	3,975	333	56	749	1,139	944	4,684
Trimester 2:																		
Maximum	125,000	1,250	2,500	3,500	1,440	13,125	10,250	46,250	11,750	990	125	10,000	642	203	1,875	7,000	2,000	11,500
Minimum	15,700	0	69	0	0	659	251	3,077	1,575	18	0	1,686	0	0	251	314	250	1,037
Average	41,518	173	462	446	251	3,229	2,623	15,415	5,441	209	47	4,467	245	73	797	1,803	835	4,675
Trimester 3:																		
Maximum	70,000	635	1,460	1,050	700	7,937	4,900	29,400	8,680	700	191	5,400	732	210	3,937	8,636	2,730	11,900
Minimum	16,900	0	0	51	0	391	340	4,901	394	0	0	1,318	0	0	51	51	119	1,329
Average	33,937	96	341	362	167	2,138	1,879	11,819	4,613	228	49	3,719	194	61	1,050	1,865	836	4,480
Pregnant women:																		
Maximum	125,000	1,250	2,500	3,500	1,440	13,125	10,250	46,250	11,750	1,140	197	10,000	965	210	3,937	8,636	2,730	11,900
Minimum	14,400	0	0	0	0	172	251	2,189	394	0	0	1,318	0	0	51	51	28	1,037
Average	36,764	115	393	366	209	2,552	2,211	10,415	5,111	288	56	4,045	246	64	886	1,662	863	4,599
Nonpregnant women:																		
Maximum	46,000	279	736	630	544	4,140	4,324	14,490	7,084	642	184	6,520	717	122	1,396	2,904	1,089	6,534
Minimum	7,550	0	11	0	0	168	168	1,091	1,132	60	0	1,721	32	0	62	134	43	1,081
Average	23,100	89	251	147	147	1,568	1,437	6,048	3,565	246	53	3,428	312	28	616	1,199	453	3,578

sedimentation rates of the blood of healthy nonpregnant women (tables 5 and 6) agree well with the values previously established,[8] and the sedimentation rates of sternal marrow (tables 1 and 5) have apparently not been previously determined. Our results are summarized in table 11. There seems to be a definite tendency for the sedimentation rates to be lower in the marrow than in the blood of the same person. The reason

TABLE 10.—*Summary of Average and Range of Values for Sternal Marrow of Pregnant and of Nonpregnant Women from This Study as Compared with the Normal Range for Sternal Marrow as Determined by Young and Osgood* [1]

	Normal Range (Male)	Average per Cu. Mm.	Range (Nonpregnant Women)	Average per Cu. Mm.	Range (Pregnant Women)	Average per Cu. Mm.
Total nucleated cell count	6,000 to 60,000 per cu. mm.		7,750 to 46,000 per cu. mm.	23,100	14,400 to 125,000 per cu. mm.	36,760
Granuloblasts	0.0 - 2.0%	0.44%	0.0 - 0.8%	0.3%	0.0 - 1.0%	0.24%
Progranulocytes, type A	0.0 - 5.0	1.48	0.1 - 2.2	1.0	0.0 - 2.3	0.93
Progranulocytes, type S	0.0 - 5.0	1.68	0.0 - 1.4	0.5	0.0 - 2.8	0.82
Eosinophilic granulocytes	0.0 - 2.0	0.64	0.0 - 1.5	0.5	0.0 - 2.6	0.40
Neutrophilic granulocytes	0.0 -10.0	0.86	1.4 -11.0	6.0	1.2 -12.5	6.25
Neutrophilic metagranulocytes	1.0 -10.0	7.4	1.4 - 9.4	5.6	1.6 - 9.0	5.46
Rhabdocytes	15.0 -35.0	24.1	12.4 -34.2	23.7	15.2 -47.6	33.3
Lobocytes	7.0 -25.0	13.3	10.4 -31.0	16.6	1.6 -37.6	15.7
Eosinophils	0.0 - 2.6	0.8	0.2 - 6.0	1.3	0.0 - 6.0	0.88
Basophils	0.0 - 0.2	0.1	0.0 - 0.8	0.3	0.0 - 1.0	0.2
Lymphocytes	4.0 -16.0	10.6	9.2 -30.4	16.8	4.5 -28.0	12.7
Monocytes	0.0 - 5.0	2.06	0.0 - 3.5	1.4	0.0 - 3.0	0.77
Karyoblasts	0.0 - 0.2	....	0.0 - 0.4	0.1	0.0 - 1.0	0.17
Prokaryocytes	0.0 - 5.0	1.5	0.6 - 4.0	2.5	0.3 - 6.2	2.37
Karyocytes	2.0 -15.0	7.0	1.3 - 8.0	5.0	0.3 -13.6	4.3
Metakaryocytes	2.0 -10.0	5.0	0.4 - 3.2	1.9	0.2 - 7.0	2.26
Disintegrated cells	12.8 -31.8	20.8	10.5 -24.0	16.2	5.5 -23.6	12.93

TABLE 11.—*Comparison of Sedimentation Rates of Blood and of Sternal Marrow in the Three Trimesters of Pregnancy and for Nonpregnant Women*

	Trimester 1		Trimester 2		Trimester 3		Nonpregnant	
	Blood	Sternal Marrow	Blood	Sternal Marrow	Blood	Sternal Marrow	Blood	Sternal Marrow
Minimum	1/6	0/1	1/6	0/1	2/13	0/2	0/2	0/0
Maximum	8/38	5/25	10/52	8/41	15/65	12/56	6/38	4/35
Average	2/14	2/9	5/29	3/17	7/36	4/24	1/8	1/4

for this is not apparent. Possibly it has to do with the protein-forming function of marrow cells.

SUMMARY

A study of the hematology of the blood and sternal marrow of 40 pregnant and 24 healthy nonpregnant women is summarized in the tables. The ranges of values given in table 10 should prove useful in interpreting the results of studies of the marrow of pregnant and nonpregnant young women.

8. Haskins, H. D.; Trotman, F. E.; Osgood, E. E., and Mathieu, A.: A Rapid Method for Determination of the Sedimentation Rate of the Red Cells with Results in Health and Disease, J. Lab. & Clin. Med. **16**:487, 1931. Osgood,[2] pp. 223 and 430.

PHOSPHATASE ACTIVITY IN CHRONIC ARTHRITIS

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The presence of a ferment, phosphatase, in the bones of young rats was demonstrated by Robison [1] in 1932. This ferment hydrolyzes the phosphoric esters of hexosephosphate, glycerophosphate and nucleoprotein. One of the resulting products of such hydrolysis is inorganic phosphorus. Therefore, this ferment plays an important role in the deposition of calcium in bone, in carbohydrate metabolism, in renal metabolism and indirectly in the maintenance of the proper hydrogen ion concentration of blood. Its ubiquitous nature in body tissues has been shown by Bodansky [2] and Kay.[3]

So complex are the physiologic functions of phosphatase that the complexity can be matched only by the chemical complexity of the liver itself. All investigators have found an increase of serum phosphatase in such diverse diseases as osteitis deformans,[4] hyperparathyroidism,[5] rickets [6] and obstructive jaundice.[6] The exact significance of

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1. Robison, R.: The Significance of Phosphoric Esters in Metabolism, New York, New York University Press, 1932.

2. Bodansky, A.: Non-Osseous Origins of Serum Phosphatase: Its Increase After Ingestion of Carbohydrates, J. Biol. Chem. **104**:473, 1934.

3. Kay, H. D.: Phosphatase in Bone Diseases, J. Biol. Chem. **89**:249, 1930.

4. Woodard, H. Q.; Twombly, G. H., and Coley, B. L.: A Study of the Serum Phosphatase in Bone Disease, J. Clin. Investigation **15**:193, 1936. Morris, N., and Pedau, O. D.: Plasma Phosphatase in Disease: A Review, Quart. J. Med. **6**:211, 1937. Bodansky, A.: Significance of Phosphatase Variations, J. Biol. Chem. **105**:11, 1934. Roberts, W. M.: Variations in the Phosphatase Activity of the Blood in Disease, Brit. J. Exper. Path. **11**:90, 1930.

5. Roe, J. H., and Whitmore, E. R.: Clinico-Pathologic Application of Serum Phosphatase Determinations, with Special Reference to Lesions of the Bones, Am. J. Clin. Path. **8**:233, 1938.

6. Roberts, W. M.: Blood Phosphatase and the van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, Brit. M. J. **1**:734, 1933. Cantarow, A.: Review of Phosphatase Activity, and Calcium and Electrolyte Metabolism, Internat. Clin. **1**:270, 1936.

this increase is unknown. Regarding other conditions, notably chronic atrophic arthritis and the healing of bone fractures, dissimilar opinions are held. Kay [7] and also Bodansky and Jaffe [8] have found an increase in serum phosphatase during repair of bone fractures, whereas Mitchell,[9] in a careful study of 75 cases, has found a normal or only slightly elevated value for serum phosphatase. Although no critical analyses of

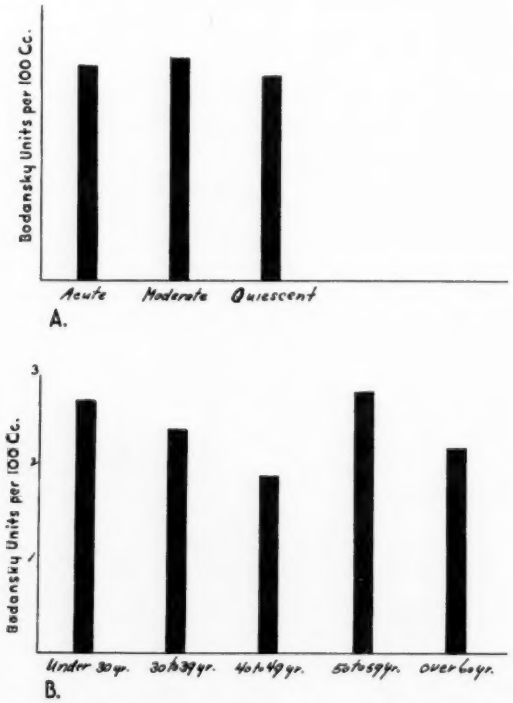

Chart 1.—Average phosphatase content of the serum for patients with atrophic arthritis grouped (*A*) according to their condition at the time of testing and (*B*) according to age.

serum phosphatase in chronic arthritis appear in the literature, Kolmer and Boerner [10] reported a high value for serum phosphatase in cases

7. Kay, H. D.: Plasma Phosphatase: The Enzyme in Disease, Particularly in Bone Disease, J. Biol. Chem. **89**:249, 1930.

8. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: Serum Phosphatase in Diseases of the Bone; Interpretation and Significance, Arch. Int. Med. **54**:88 (July) 1934.

(Footnotes continued on next page)

of chronic arthritis, and Abrams and Bauer [11] reported a normal value in cases of atrophic arthritis.

The well known pathologic processes of localized osteoporosis associated with chronic atrophic arthritis and the hypertrophic changes of cartilage and bone associated with hypertrophic arthritis suggest the possibility that some abnormal change in serum phosphatase may occur with these conditions. This study is a critical analysis of the values for serum phosphatase for 44 patients with atrophic arthritis and for control groups of patients with hypertrophic arthritis, patients with osteitis deformans and normal healthy persons. The patients with atrophic arthritis were divided into four groups on the basis of the grade of involvement. The group with involvement of grade 1 includes patients having articular pains and stiffness with an increased sedimentation rate

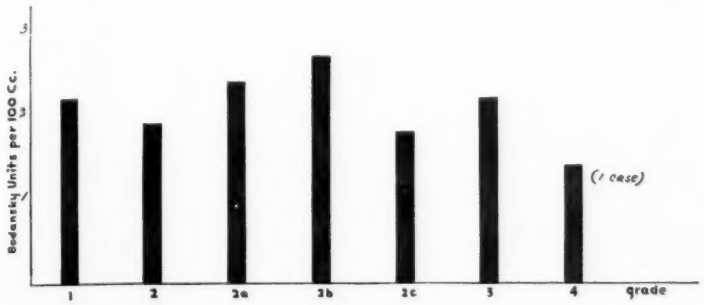

Chart 2.—Average phosphatase content of the serum for patients with atrophic arthritis grouped according to the grade of involvement. The figures at the bottom of the chart, denoting the grades of involvement, are to be interpreted as follows: *1*, articular pain; *2*, swelling of the soft tissues; *2a*, *2b*, *2c*, gradations between *2* and *3*; *3*, definite articular deformity with early ankylosis; *4*, advanced ankylosis (the patient was an arthritic derelict).

and a shift of the Schilling count to the left but no objective signs regarding the joints. The group with involvement of grade 2 includes patients with definite swelling of the soft tissues and localized increase of temperature surrounding the joints involved. The group with involvement of grade 3 includes patients with early fibrous, cartilaginous or bony ankylosis of one or several joints but not patients confined to bed. The group with involvement of grade 4 includes patients confined

9. Mitchell, L. C.: Serum Phosphatase in Fracture Repair, Ann. Surg. **104**: 304, 1936.

10. Kolmer, J. A., and Boerner, F.: Approved Laboratory Technic, ed. 2, New York, D. Appleton-Century Company, 1938, p. 759.

11. Abrams, N. R., and Bauer, W.: The Treatment of Rheumatoid Arthritis with Large Doses of Vitamin D, J. A. M. A. **111**:1632 (Oct. 29) 1938.

TABLE 1.—*Data for Patients with Atrophic Arthritis Grouped According to Grade of Involvement*

Grade	Case No.	Sex of Patient	Age of Patient, Yr.	Duration of Disease	Condition at Time of Test	Phosphorus, Mg.	Phosphatase, Units
1	27	M	44	7 yr.	Moderate	2.8	1.9
	32	F	51	12 yr.	Moderate	2.6	2.5
	Average for group:		48	10 yr.	.....	2.7	2.2
2	3	F	35	8 mo.	Moderate	3.5	2.5
	42	F	33	25 yr.	Moderate	3.6	1.9
	11	F	51	2 yr.	Quiescent	4.2	1.6
	13	F	29	3 yr.	Quiescent	2.6	2.9
	9	F	27	1½ yr.	Quiescent	2.6	1.3
	Average for group:		35	6 yr.	.....	3.3	1.9
2a	1	F	34	4 mo.	Acute	3.3	1.4
	2	M	53	4 mo.	Acute	3.5	2.3
	8	F	59	1 yr.	Acute	3.8	3.3
	14	F	59	3 yr.	Acute	3.6	1.6
	6	F	61	1 yr.	Moderate	2.6	4.2
	30	M	63	10 yr.	Moderate	2.4	1.4
	40	F	37	21 yr.	Moderate	3.4	2.4
	18	F	65	4 yr.	Acute	3.5	3.2
	19	F	47	5 yr.	Quiescent	2.6	1.6
	Average for group:		53	9 yr.	.....	3.1	2.4
2b	10	M	59	1½ yr.	Acute	4.3	5.3
	33	M	50	12 yr.	Acute	2.4	1.6
	37	M	45	16 yr.	Acute	3.0	1.4
	39	F	32	19 yr.	Acute	3.4	2.2
	38	F	38	16 yr.	Moderate	3.4	1.9
	21	F	38	5 yr.	Moderate	2.5	1.8
	10a	M	50	1½ yr.	Moderate	3.5	4.2
	5	F	55	1 yr.	Quiescent	2.6	3.4
	12	F	53	2 yr.	Quiescent	3.1	1.7
	12a	F	53	2 yr.	Quiescent	3.5	2.1
	22	M	39	5 yr.	Quiescent	3.2	3.4
	23	F	17	6 yr.	Quiescent	3.4	3.6
	Average for group:		45	7 yr.	.....	2.6	2.7
2c	31	F	27	11 yr.	Acute	3.4	1.8
	31a	F	27	11 yr.	Moderate	2.8	1.8
	Average for group:		27	11 yr.	.....	3.1	1.8
3	4	F	19	8 mo.	Acute	3.2	2.8
	7	F	38	1 yr.	Acute	3.0	2.1
	7a	F	38	1 yr.	Acute	3.5	1.7
	16	M	38	4 yr.	Acute	3.1	3.4
	20	F	44	5 yr.	Acute	3.7	1.8
	29	F	44	10 yr.	Acute	3.5	4.0
	35	F	47	14 yr.	Acute	4.6	1.0
	15	M	24	3 yr.	Moderate	3.3	2.0
	17	M	43	4 yr.	Moderate	3.5	2.9
	24	F	59	6 yr.	Moderate	4.0	2.9
	25	F	65	7 yr.	Moderate	3.3	3.0
	44	F	60	30 yr.	Moderate	2.9	1.7
	36	F	66	15 yr.	Acute	3.2	1.6
	26	F	38	7 yr.	Quiescent	3.5	2.6
	34	M	61	12 yr.	Quiescent	3.6	2.1
	35a	F	47	14 yr.	Quiescent	3.5	1.0
	43	F	62	30 yr.	Quiescent	2.7	1.3
	Average for group:		47	10 yr.	.....	3.4	
4	28	M	60	10 yr.	Acute	3.0	1.4

to bed; i. e., patients with ankylosis sufficient to prevent them from being ambulatory. Gradations of disease between these four grades have been designated with letters of the alphabet. The average values for serum phosphatase according to the various grades of involvement were: grade 1, 2.2 Bodansky units; grade 2, 1.9 Bodansky units; grade 3a, 2.4 Bodansky units; grade 2b, 2.7 Bodansky units; grade 2c, 1.8 Bodansky units; grade 3, 2.2 Bodansky units, and grade 4 (1 patient), 1.4 Bodansky units. Study of these groups of patients fails to indicate conclusively any relation between the degree of articular destruction and the level of serum phosphatase.

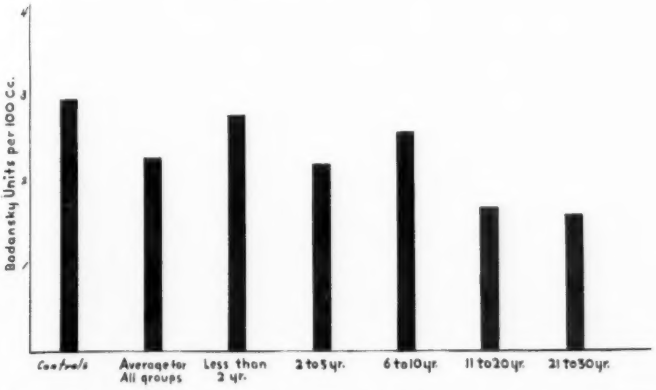

Chart 3.—Average phosphatase content of the serum for patients with atrophic arthritis grouped according to the duration of the disease.

These patients were also studied according to the duration of the disease. The average value for serum phosphatase for the patients with a definite history of atrophic arthritis of less than two years' duration was 2.8 units; two to five years' duration, 2.2 units; of six to ten years' duration, 2.6 units; of eleven to twenty years' duration, 1.7 units; and of twenty-one to thirty years' duration, 1.6 units. Therefore, there exists an inverse ratio between the duration of the disease and the level of serum phosphatase. Gutman and his associates [12] have shown that the phosphatase content of the serum is slightly increased in generalized osteoporosis in young and middle-aged persons but not in the aged; that is, loss of vitality of bone tissue equals loss in phosphatase activity. At first glance one might surmise that the inverse ratio between the duration of the disease and the value for serum phosphatase may be due to the age of the more chronic process rather than to any physio-

12. Gutman, A. B.; Swenson, P. C., and Parsons, W. B.: Differential Diagnosis of Hyperparathyroidism, J. A. M. A. **103**:87 (July 14) 1934.

TABLE 2.—*Data for Patients with Atrophic Arthritis Grouped According to the Duration of the Disease*

Case No.	Sex of Patient	Age of Patient, Yr.	Duration of Disease	Condition at Time of Test	Grade of Involvement	Phosphorus, Mg.	Phosphatase, Units
Less than 2 years:							
1	F	34	4 mo.	Acute	2a	3.3	1.4
2	M	53	4 mo.	Acute	2a	3.5	2.3
3*	F	35	8 mo.	Moderate	2	3.5	2.5
4	F	19	8 mo.	Subacute	3	3.2	2.8
5	F	55	1 yr.	Quiescent	2b	2.6	3.4
6	F	61	1 yr.	Moderate to acute	2a	2.6	4.2
7	F	38	1 yr.	Acute	3	3.0	2.1
7a	F	38	1 yr.	Acute	3	3.5	1.7
8†	F	30	1 yr.	Acute	2a	3.8	3.3
9‡	F	27	1½ yr.	Quiescent	2	2.6	1.3
10§	M	59	1½ yr.	Acute	2b	4.3	5.3
10a§	M	59	1½ yr.	Moderate to acute	2b	3.5	4.2
	Averages:	41	.....	.....	.....	3.3	2.8
From 2 to 5 years:							
11	F	51	2 yr.	Quiescent	2	4.2	1.6
12	F	53	2 yr.	Quiescent	2b	3.1	1.7
12a	F	53	2 yr.	Quiescent	2b	3.5	2.1
13	F	29	3 yr.	Quiescent	2	2.6	2.9
14	F	59	3 yr.	Acute	2a	3.6	1.6
15	M	24	3 yr.	Moderate to acute	3	3.3	2.0
16	M	38	4 yr.	Acute	3	3.1	3.4
17	M	43	4 yr.	Moderate	3	3.5	2.9
18	F	65	4 yr.	Subacute	2a	3.5	3.2
19	F	47	5 yr.	Quiescent	2a	2.6	1.6
20	F	44	5 yr.	Subacute	3	3.7	1.8
21	F	38	5 yr.	Moderate	2b	2.5	1.8
22	M	39	5 yr.	Quiescent	2b	3.2	3.4
	Averages:	46	.....	.....	.....	3.3	2.2
From 6 to 10 years:							
23	F	17	6 yr.	Quiescent	2b	3.4	3.6
24	F	59	6 yr.	Moderate to acute	3	4.0	2.9
25	F	65	7 yr.	Moderate to acute	3	3.3	3.0
26	F	38	7 yr.	Quiescent	3	3.5	2.6
27	M	44	7 yr.	Moderate	1	2.8	1.9
28	M	60	10 yr.	Very acute	4	3.0	1.4
29	F	44	10 yr.	Acute	3	3.5	4.0
30	M	63	10 yr.	Moderate to quiescent	2a	2.4	1.4
	Averages:	49	.....	.....	.....	3.2	2.6
From 11 to 20 years:							
31	F	27	11 yr.	Acute	2c	3.4	1.8
31a	F	27	11 yr.	Moderate	2c	2.8	1.8
32	F	51	12 yr.	Moderate	1	2.6	2.5
33	M	50	12 yr.	Acute	2b	2.4	1.6
34	M	61	12 yr.	Quiescent	3	3.6	2.1
35	F	47	14 yr.	Very acute	3	3.6	1.0
35a	F	47	14 yr.	Quiescent	3	3.5	1.0
36#	F	66	15 yr.	Acute	3	3.2	1.6
37	M	45	16 yr.	Acute	2b	3.0	1.4
37a	M	45	16 yr.	Quiescent	2b	3.5	1.7
38	F	38	16 yr.	Moderate	2b	3.4	1.9
39	F	32	19 yr.	Subacute	2b	3.4	2.2
	Averages:	46	.....	.....	.....	3.3	1.7
From 21 to 30 years:							
40	F	37	21 yr.	Moderate to quiescent	2a	3.4	2.4
42	F	33	25 yr.	Moderate	2	3.6	1.0
43	F	62	30 yr.	Quiescent	3	2.7	1.3
44	F	60	30 yr.	Moderate to acute	3	2.9	1.7
	Averages:	48	.....	.....	.....	3.2	1.6
Averages for all groups:		47	.....	.....	.....	3.3	2.3
Male patients			.....	.....	.....	3.2	2.5
Female patients			.....	.....	.....	3.3	2.2

* Complicated by mitral stenosis.
† Complicated by hyperthyroidism.
‡ Complicated by pregnancy.
§ Complicated by carcinoma of the prostate with secondary involvement of lung and bone tissue.
\# Complicated by postoperative hypothyroidism.

pathologic change associated with chronic atrophic arthritis. However, the average age of the patients who had had chronic arthritis for less than two years was 41; for two to five years, 46; for six to ten

TABLE 3.—*Data for Patients with Atrophic Arthritis Grouped According to Condition at Time of Test*

Case No.	Sex of Patient	Age, Yr.	Duration	Grade of Involvement	Phosphorus, Mg.	Phosphatase, Units
			Acutely Active Arthritis at Time of Test			
1	F	34	4 mo.	2a	3.3	1.4
2	M	53	4 mo.	2a	3.5	2.3
4	F	19	8 mo.	3	3.2	2.8
7	F	38	1 yr.	3	3.0	2.1
7a	F	38	1 yr.	3	3.5	1.7
8	F	59	1 yr.	2a	3.8	3.3
10	M	59	1½ yr.	2b	4.3	5.3
14	F	59	3 yr.	2a	3.6	1.6
16	M	38	4 yr.	3	3.1	3.4
18	F	65	4 yr.	2a	3.5	3.2
20	F	44	5 yr.	3	3.7	1.8
28	M	60	10 yr.	4	3.0	1.4
29	F	44	10 yr.	3	3.5	4.0
31	F	27	11 yr.	2c	3.4	1.8
33	M	50	12 yr.	2b	2.4	1.6
35	F	47	14 yr.	3	4.6	1.0
36	F	66	15 yr.	3	3.2	1.6
37	M	45	16 yr.	2b	3.0	1.4
39	F	32	19 yr.	2b	3.4	2.2
Average for group					3.4	2.3
			Moderately Active Arthritis at Time of Test			
3	F	35	8 mo.	2	3.5	2.5
6	F	61	1 yr.	2a	2.6	4.2
10a	M	59	1½ yr.	2b	3.5	4.2
15	M	24	3 yr.	3	3.3	2.0
17	M	43	4 yr.	3	3.5	2.9
21	F	38	5 yr.	2b	2.5	1.8
24	F	59	6 yr.	3	4.0	2.9
25	F	65	7 yr.	3	3.3	3.0
27	M	44	7 yr.	1	2.8	1.9
30	M	63	10 yr.	2a	2.4	1.4
31a	F	27	11 yr.	2c	2.8	1.8
32	F	51	12 yr.	1	2.6	2.5
38	F	38	16 yr.	2b	3.4	1.9
40	F	37	21 yr.	2a	3.4	2.4
42	F	33	25 yr.	2	3.6	1.0
44	F	60	30 yr.	3	2.9	1.7
Average for group					3.1	2.4
			Quiescent Arthritis at Time of Test			
5	F	55	1 yr.	2b	2.6	3.4
9	F	27	1½ yr.	2	2.6	1.3
11	F	51	2 yr.	2	4.2	1.6
12	F	53	2 yr.	2b	3.1	1.7
12a	F	53	2 yr.	2b	3.5	2.1
13	F	29	3 yr.	2	2.6	2.9
19	F	47	5 yr.	2a	2.6	1.6
22	M	39	5 yr.	2b	3.2	3.4
23	F	17	6 yr.	2b	3.4	3.6
26	F	38	7 yr.	3	3.5	2.6
34	M	61	12 yr.	3	3.6	2.1
35a	F	47	14 yr.	3	3.5	1.0
37a	M	45	16 yr.	2b	3.5	17.
43	F	62	30 yr.	3	2.7	1.3
Average for group					3.2	2.2

years, 49; for eleven to twenty years, 46, and for twenty-one to forty years, 48. The average age for all these groups was therefore similar, and one must conclude that the duration of the disease affects inversely the value for serum phosphatase.

The degree of articular activity in cases of chronic atrophic arthritis varies considerably. The clinical pattern is one of exacerbations and remissions. We grouped our patients into three divisions, depending on the activity of the arthritis at the time that the study of the serum phosphatase was done, that is, patients with acute arthritis, those with moderately active arthritis and those with quiescent arthritis. The phosphatase content of the serum for the first group was 2.3 units; that for the second group, 2.4 units, and that for the third group, 2.2 units.

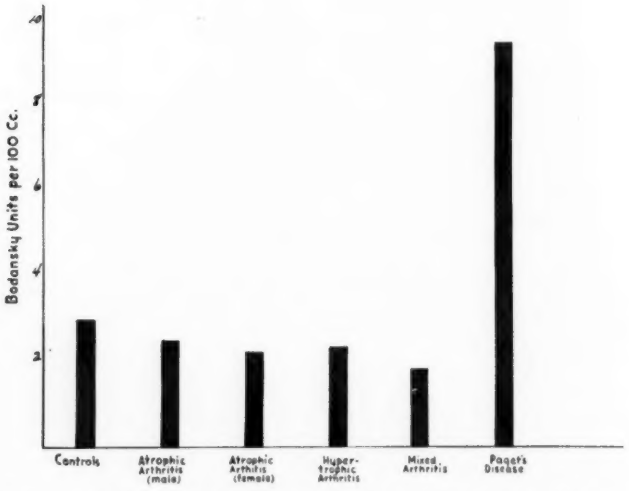

Chart 4.—Average phosphatase content of the serum for the different control groups.

We must conclude that the activity of the arthritic process does not affect the serum phosphatase.

The control groups consisted of 6 normal persons, 5 patients with osteitis deformans and a small group of patients with hypertrophic arthritis and mixed hypertrophic and atrophic arthritis. The normal persons showed an average value for serum phosphatase of 3 Bodansky units. The average value for serum phosphatase for the 5 patients with osteitis deformans (Paget's disease) was 9.46 units, the variation being 6.24 to 20.20 units. For the small group with hypertrophic arthritis and mixed hypertrophic and atrophic arthritis the values were 2.3 and 1.8 units respectively.

Our findings seem to indicate that a normal level of serum phosphatase is present in cases of chronic atrophic arthritis. The severity of involvement, the stage of the disease and the age of the patient do not affect the level. Long duration of the disease tends to diminish it.

TABLE 4.—*Data for Patients with Paget's Disease (Control Study)*

Case No.	Age of Patient, Yr.	Sex of Patient	Duration of Disease	Extent of Involvement	Phosphorus, Mg.	Phosphatase, Units
1	67	F	Unknown	Localized in skull; verified by roentgenogram	3.44	8.72
2	67	M	Unknown	Localized in skull; verified by roentgenogram; ribs and long bones normal	2.96	7.68
2 (repeated)	..	.....	.....	.....	3.44	7.04
3	73	M	20 yr.	Generalized; pyramidal head	4.60	14.12
4	81	F	36 yr.	Localized; gross change; left leg	3.52	6.24
5	69	F	10 to 15 yr.	Generalized; knee; frontal bosses markedly pyramidal; verified by roentgenogram	3.80	20.20
Averages.....					3.55	9.46

TABLE 5.—*Phosphorus and Phosphatase Content of the Serum for the Control Groups of Patients*

	Case No.	Age, Yr.	Sex	Phosphorus, Mg.	Phosphatase, Units
Normal persons	1	43	F	3.6	3.0
	2	28	F	3.3	2.3
	3	17	M	3.1	3.7
	4	24	F	2.4	3.6
	5	23	M	3.9	3.1
	6	41	F	2.5	2.5
Average.....		31		3.1	3.0
Patients with hypertrophic arthritis	45	49	F	3.1	2.6
	46	53	F	4.2	2.4
	47	54	M	3.8	1.7
	48	55	F	2.4	2.4
	49	46	M	2.5	1.6
	50	47	M	2.8	2.1
	51	65	M	3.0	3.0
	52	46	F	3.3	2.5
Average.....		52		3.1	2.3
Patients with mixed hypertrophic and atrophic arthritis	53	49	F	2.9	1.9
	54	60	F	3.8	1.3
	55	50	F	2.7	1.0
	56	56	F	3.4	1.7
	57	43	F	2.4	3.3
Average.....		52		3.1	1.8

We found the determination of the level of serum phosphatase valuable in differentiating between articular pains associated with chronic arthritis and the indefinite pains associated with osteitis deformans. It is important to remember that the ages of the patients suffering from hypertrophic arthritis and those of the patients suffering from osteitis deformans were similar. Osteitis deformans is associated in many cases with

hypertrophic arthritis, but in many others the latter condition is not present. One instance of osteitis deformans was accidentally discovered during our study of serum phosphatase. The patient was a white man aged 67, a member of the control group. He had a mild degree of hypertrophic arthritis with associated articular pains, for which he sought relief. After an increased value for serum phosphatase had been noted on two occasions, roentgenograms of the patient's skull, pelvis, ribs and long bones were taken. Findings typical of osteitis deformans were demonstrated on the films.

SUMMARY AND CONCLUSIONS

Determinations of the phosphatase content of the serum were made for 44 patients with atrophic arthritis, 8 patients with hypertrophic arthritis, 5 patients with mixed atrophic and hypertrophic arthritis and 5 patients with osteitis deformans. This same study was made of 6 healthy persons. In the only case of arthritis in which the value for serum phosphatase was above 4.2 units it was later proved that malignant tumor of the prostate gland was present, with secondary involvement of bone and lung tissue. An increase of serum phosphatase in this type of malignant disease has been described by Gutman and his co-workers.[13] Determination of the phosphatase content of the serum in cases of chronic atrophic and hypertrophic arthritis is, therefore, important in the differential diagnosis. A normal value for serum phosphatase is characteristic of chronic atrophic or hypertrophic arthritis; an abnormal value suggests the possibility of a complicating condition or an erroneous diagnosis of this condition. Determinations of the phosphatase content of the serum should be made a routine procedure in the study of diseases of the bones and joints.

Dr. E. T. Wentworth permitted us to study the patients with Paget's disease who were used as controls in this investigation.

13. Gutman, E. B.; Sproul, E. E., and Gutman, A. B.: Significance of Increased Phosphatase Activity of Bone at the Side of Osteoplastic Metastases Secondary to Carcinoma of the Prostate Gland, Am. J. Cancer **28**:485, 1936.

ELECTROCARDIOGRAPHIC FINDINGS IN CASES OF VENTRICULAR ANEURYSM

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It is the almost unanimous opinion of those who have studied aneurysm of the ventricle complicating occlusion of the coronary artery that the diagnosis of this condition is a difficult clinical task. The rarity of occurrence of the lesion has been somewhat overemphasized. Libman [1] reported that it was found fifteen times as frequently as Hodgkin's disease, and Applebaum and Nicolson [2] found aneurysm of the ventricle to have been present in 57 (or 38 per cent) of 150 cases of occlusive disease of the coronary arteries of the atherosclerotic group. Of the 57 aneurysms, 56 were located in the left ventricle.

Pletnew [3] has shown the difficulty of diagnosis by purely physical means; he reported 0.5 per cent successful diagnoses in 300 cases. Kahn,[4] in 1922, stated that roentgenographic and fluoroscopic examination are of little aid in the diagnosis of this condition, but more recently several authors [5] have detected the sacculation by roentgenographic

From the Mount Zion Hospital and the University of California Medical Service of the San Francisco Hospital and the Department of Public Health.

1. Libman, E.: Methods of Physical Examination, with Special Reference to Painful Disease of the Thorax and Abdomen, Proc. Inter-State Post-Grad. M. A., North America (1926), 1927, p. 60.

2. Applebaum, E., and Nicolson, G.: Occlusive Diseases of the Coronary Arteries, Am. Heart J. **10**:662, 1935.

3. Pletnew, D. D.: Lässt sich ein Aneurysma der Herzventrikel intra vitam feststellen? Ztschr. f. klin. Med. **104**:378, 1926.

4. Kahn, M. H.: Aneurysm of the Left Ventricle, Am. J. M. Sc. **163**:839, 1922.

5. (*a*) Fogel, E. I.: Aneurysm of the Left Ventricle Following Coronary Infarction in a Living Patient, J. A. M. A. **100**:39 (Jan. 7) 1933. (*b*) Steel, D.: The Roentgen Diagnosis of Cardiac Aneurysms, ibid. **102**:432 (Feb. 10) 1934. (*c*) Shookhoff, C., and Douglas, A. H.: A Case of Acute Coronary Occlusion with Roentgenographic Evidence of the Early Development of an Aneurysm of the Left Ventricle, Am. Heart J. **7**:95, 1931. (*d*) Strandell, B.: A Contribution to the Diagnosis of Aneurysm of the Heart, Acta med. Scandinav. **74**:148, 1930. (*e*) Ellman, P.: Angina with Recent Coronary Thrombosis, Myocardial Infarction and Cardiac Aneurysm, Proc. Roy. Soc. Med. **26**:139, 1932. (*f*) Sigler, L. H., and Schneider, J. J.: Diagnosis of Cardiac Aneurysms with Report of Two Cases,

(Footnote continued on next page)

methods. Sigler and Schneider [5f] stated that the electrocardiogram is of no specific diagnostic value in disclosing a cardiac aneurysm. However, these authors did mention the fact that in some instances major deflections directed downward in the second and third leads of the standard electrocardiogram with low voltage upward in lead I may be found.

Because of the grave prognosis of this complication of myocardial infarction and its frequent termination by sudden death with or without

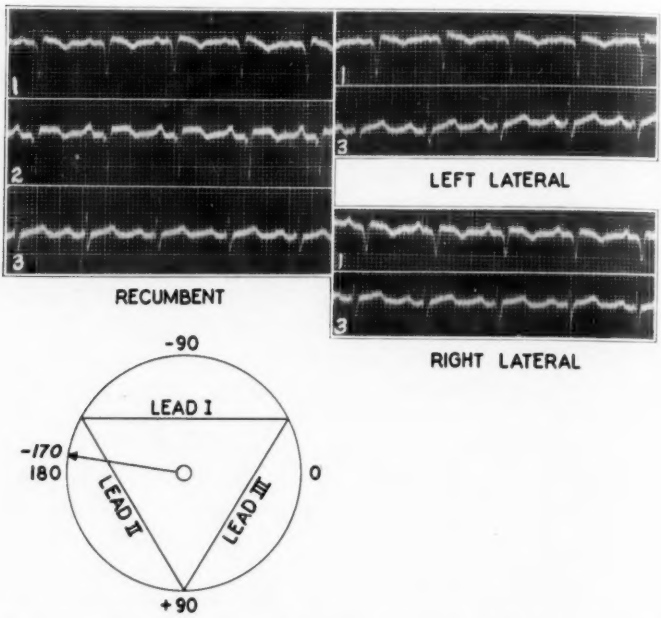

Fig. 1 (case 1).—The downward direction of the major deflection with inversion of the T wave and an upright P wave in lead I occurred four weeks after the initial acute occlusion of the coronary artery. The Einthoven triangle illustrates the right axis deviation. The effect of placing the patient in the lateral positions is seen to be negligible. This recording is essentially the same as that taken eight months after the original occlusion of the coronary artery.

rupture, it would seem expedient to utilize all possible diagnostic means to ascertain its presence if such a consequence could thereby be forestalled.

Ann. Int. Med. **8**:1033, 1935. (*g*) Ball, D.: Aneurysm of the Heart, Am. Heart J. **16**:203, 1938. (*h*) Harvier, P., and Caroli, J.: Sur un cas d'aneurysme de la pointe du coeur, Paris méd. **77**:30, 1930. (*i*) East, T.: Aneurysm of the Left Ventricle, Proc. Roy. Soc. Med. **26**:518, 1933.

We believe that the electrocardiogram may be of considerable diagnostic value. In several cases we have observed certain cardiographic changes that may be considered a presumptive sign of cardiac aneurysm, and in a slightly greater number of cases we found changes that appeared to be rather suggestive evidence of this lesion.

The contention that study of the electrical activity of the heart may be a valuable aid in the diagnosis of this condition is supported by an analysis of the cases previously reported with accompanying electrocardiograms, together with 5 examples of aneurysm of the ventricle following occlusion of the coronary artery, which we shall present.

The previously published reports show that in 23.5 per cent of the tracings there is a downward direction of the major deflection in lead I. Associated with this finding is inversion of the T wave and an upright P wave in the first lead, the ventricular complex being upright in lead III (fig. 1). By depicting such curves on the Einthoven equilateral triangle, one finds that the electrical axis is in the range of — 150 to 180 degrees. In 2 of the 5 cases in our series (40 per cent) this type of record appeared. In 2 other cases of our series (40 per cent), the left axis deviation that has been observed previously in some cases of cardiac aneurysm was found. The left axis deviation is shown on the triangle in figure 4. In this group and in 35.3 per cent of cases reported in the literature, the major deflections were directed downward in leads II and III, with or without low amplitude of the ventricular complex in the first lead (fig. 4).

Cases 1 and 2, which will be described briefly, are examples of those in which right axis deviation occurs (the S_1 type of cardiogram), and case 3 is presented to illustrate those in which left axis deviation is observed (the $S_{2,3}$ type).

REPORT OF CASES

Case 1.—F. F., a 39 year old Russian man, entered the San Francisco Hospital on Nov. 21, 1937, with the complaint of a heavy, nonradiating sensation in the chest of several hours' duration, coming on while at rest. This was associated with marked weakness and nausea. Physical examination showed the patient to be dyspneic, suffering severe pain and clawing at his chest. The temperature was 97 F.; the pulse was barely perceptible, and the blood pressure was so low as not to be obtainable. The heart was normal to percussion, but the sounds were faint. The leukocyte count was 14,500 per cubic millimeter; the sedimentation rate was 20 mm. in one hour (Linzenmeier method), and the Wassermann reaction of the blood was negative.

The next day the temperature rose to 101 F., and the blood pressure was recorded as 98 mm. of mercury systolic and 80 diastolic. The patient complained of moderate precordial pain at that time. An electrocardiogram taken four days after his entry (Nov. 25, 1937) is presented in figure 2.

After transient monoplegia of the right arm, he was fairly comfortable until four weeks later, when there was a recurrence of substernal pain with an associated febrile reaction. This was accompanied by changes in the electrocardiogram, namely, downward direction of the ventricular complex in lead II and inversion of the T waves in leads I and II.

Several minor recurrences of pain were noted six weeks after the initial attack. At this time it was found that the apical impulse was palpable in the fifth interspace, 9 cm. to the left of the midsternal line. A presystolic gallop rhythm was detected. The blood pressure was 95 mm. of mercury systolic and 60 diastolic. There was no evidence of the monoplegia. The electrocardiogram was unchanged.

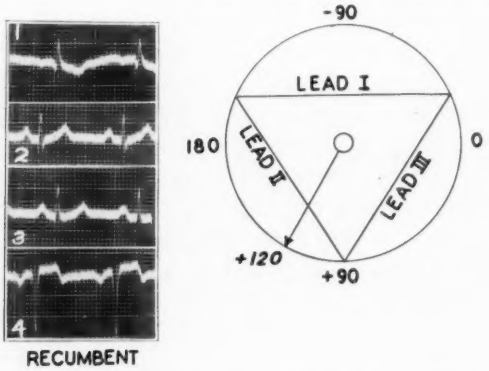

Fig. 2 (case 1).—An electrocardiogram taken four days after the initial acute occlusion of the coronary artery, showing the downward direction of the ventricular complex in lead I, with an upright T wave. The right axis deviation is represented on the Einthoven equilateral triangle.

Two months later the patient was admitted to the Mount Zion Hospital with precordial pain which had begun several hours before. Examination showed the apical impulse to be in the sixth interspace 12 cm. to the left of the midsternal line and 3 cm. inside the left border of cardiac dulness. Gallop rhythm was detected, and the blood pressure was as before, without alternation of the pulse. The electrocardiogram was essentially the same as that shown in figure 1. A roentgenogram of the chest was taken in an attempt to secure further evidence of ventricular aneurysm because of the suggestive cardiographic findings. The roentgenologist, Dr. Joseph Levitin, reported at this time that the appearance of the cardiac shadow was consistent with aneurysm of the left ventricle. This film was taken four months after the first coronary occlusion. Eight months after the first attack, the lesion was obvious, as is shown in figure 3. At that time the electrocardiogram was unchanged from that taken four weeks after the original acute thrombosis.

At the time of writing, ten months after the initial occlusion of the coronary artery, the patient is having mild anginal pain only on effort.

Case 2.—J. M., a 49 year old Irishman, entered the University of California Medical Service of the San Francisco Hospital with a history of dyspnea of six months' duration, which had begun immediately after an attack of precordial pain for which he had been hospitalized for only a few days. Up to the time of entry he had been employed as a laborer. On examination, he was found to be an orthopneic, pyknic man, without edema. There were signs of bilateral pleural effusion, and subcrepitant rales were audible at each pulmonary base. The heart was enlarged to the left, with the apical impulse 9 cm. to the left of the midsternal line in the fifth interspace. The cardiac sounds were normal except for a gallop rhythm; the arterial tension was 96 mm. of mercury systolic and 64 diastolic without pulsus alternans. The liver was palpable and tender. Roentgenographic examination showed signs of bilateral pleural effusion and chronic passive congestion of the lungs, obscuring the cardiac shadow. The Wassermann reaction of the blood

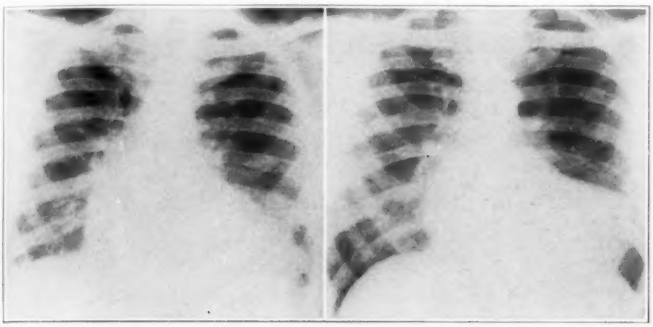

Fig. 3 (case 1).—Roentgenograms taken four and eight months, respectively, after the initial acute occlusion of the coronary artery, showing the increasing size of the aneurysm of the left ventricle.

was negative. The electrocardiogram showed a rate of 120, a sinus mechanism, a PR interval of 0.24 second and a normal QRS time, with the chief initial ventricular complex deflected downward in lead I but upright in leads II and III. The T waves were upright in leads II and III but not in lead I. The representation on the Einthoven triangle of deviation of the axis was — 160. Five days after entry the patient died. The anatomic diagnoses were: coronary thrombosis, recent and old, of the left anterior branches; mural thrombus in the left ventricle; aneurysmal dilatation of the left ventricle; chronic passive congestion of all organs; ascites, and bilateral hydrothorax.

Case 3.—E. S., a 54 year old diabetic woman, had noted dyspnea on exertion for one year, with associated tachypnea when at rest. She failed to recall having had any severe or prolonged precordial pain but had had numerous minor attacks of anginal pain on effort. Physical examination showed an orthopneic woman

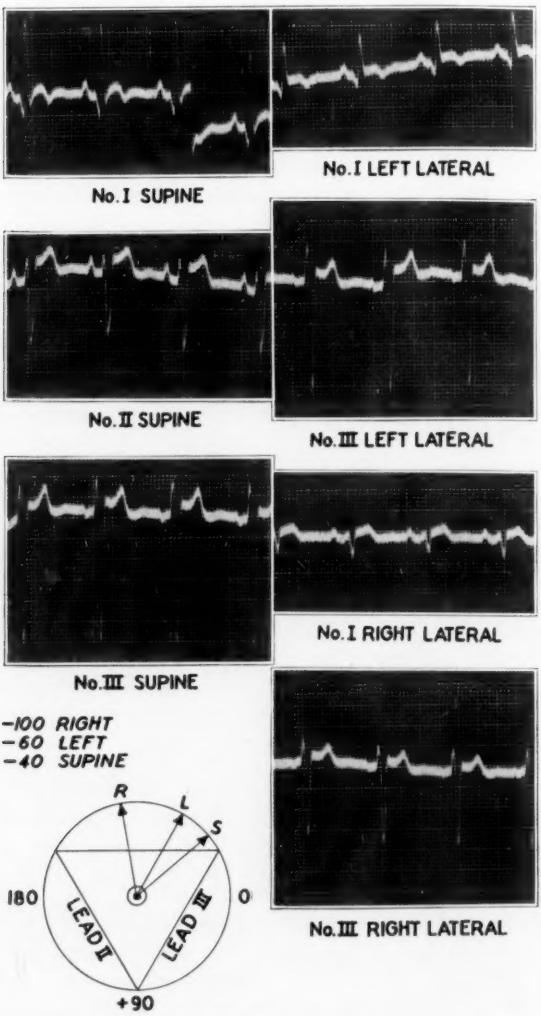

Fig. 4 (case 3).—An example of the downward direction of the major deflections in leads II and III, with representation by means of the Einthoven triangle of the axis deviation with the patient in the lateral decubitus positions, as well as supine. This record was made one year after the onset of dyspnea which followed recurrent attacks of precordial pain coming on with effort.

with edema of the ankles and signs of fluid at the bases of both lungs. The heart was greatly enlarged to the left, with the point of maximal impulse in the mid-axillary line in the sixth interspace. There was a definite gallop rhythm but no pericardial friction rub. The blood pressure was 175 mm. of mercury systolic and 110 diastolic, with intermittent periods of alternation of the pulse. The results of hemanalysis were not remarkable, and the urinary findings were normal. Transient left hemiplegia was observed twice, on one occasion lasting four hours and on the other two days. One year later, after several attacks of congestive failure, the patient died. The pathologic diagnoses were: cardiac hypertrophy with aneurysmal dilatation of the lower portion of the left ventricle; adherent mural thrombus filling the sac, and chronic obliterative pericarditis. Electrocardiograms and a roentgenogram are shown in figures 4 and 5.

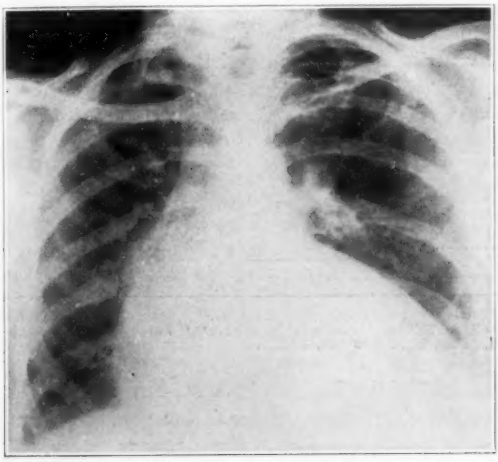

Fig. 5 (case 3).—A roentgenogram taken one year after the onset of dyspnea following recurrent attacks of precordial pain coming on with effort, illustrating the aneurysmal dilatation of the left ventricle.

COMMENT

The first 2 of these cases illustrate the electrocardiographic syndrome that was observed to accompany ventricular aneurysm in 27.3 per cent of all cases analyzed. It is of interest to note that recordings made with the patient in the recumbent and in the left and right lateral positions showed no remarkable alteration of the electrical axis of the heart. The electrocardiogram in case 3 is 1 of 2 examples of the $S_{2,3}$ type, which was obtained in 36.4 per cent of all the cases of aneurysm that were studied.

When this downward direction of the major deflections of leads II and III was found, accompanied by an abnormal increase in the QRS

time, notching of the ventricular complexes and T waves that were directed opposite to the major deflections, left bundle branch block was the obvious diagnosis. Conditions of this type were therefore excluded from the group. Their incidence is shown in the accompanying table. It is readily apparent that such tracings can be of no diagnostic value in detecting the presence or absence of cardiac aneurysm. Complete bundle branch block appeared in none of our cases.

In 1 of our cases an electrocardiogram was obtained which, though consistent with occlusion of the coronary artery, did not fall into either of the two diagnostic groups and was not consistent with the diagnosis of bundle branch block.

The table illustrates the frequency of occurrence of the various types of electrocardiographic record. The cases selected from the previously published reports include only those that were considered to be definite instances of ventricular aneurysm and that were illustrated by electro-

Types of Electrocardiogram in Cases of Aneurysm of the Left Ventricle Following Occlusion of the Coronary Artery

	Number of Cases	S_1	S_2	Bundle Branch Block	All Others
Previously reported*....	17	4 (23.5%)	6 (35.3%)	4 (23.5%)	3 (17.6%)
Present series.....	5	2 (40.0%)	2 (40.0%)	.....	1 (20.0%)
Total.....	22	6 (27.3%)	8 (36.4%)	4 (18.2%)	4 (18.2%)

* Kahn.[4] Fogel.[5a] Shookhoff and Douglas.[5c] Strandell.[5d] Ellman.[5e] Sigler and Schneider.[5f] Ball.[5g] Scherf, D., and Erlsbacher, O.: Zur Symptomatologie des partiellen Herz-aneurysmas, Med. Klin. **30**: 1687, 1934. Harvier and Caroll.[5h] East.[5i]

cardiograms. In 4 of the 5 cases of our series the condition was proved by pathologic examination to be sacculation resulting from myocardial infarction attendant on occlusion of the coronary artery. The diagnosis in case 1 would seem to be sufficiently well substantiated by the roentgenogram (fig. 3) to permit inclusion in the series.

It cannot be stated with certainty that a downward major deflection with upright P wave and inverted T wave in lead I is an exaggerated Q_1, T_1 type of curve associated only with acute occlusion of the anterior coronary artery. The last tracing in case 1 of our series, obtained ten months after the occlusion, is not dissimilar to that taken four weeks after the initial occurrence of thrombosis, which we believe to have been the event directly leading to the aneurysmal dilatation of the left ventricle. This perpetuation of the right axis deviation also was observed in several cases previously reported.

The electrocardiographic differentiation of ventricular aneurysms producing the S_1 type of electrocardiogram from cor pulmonale and mitral stenosis can be based on the relative rarity of inversion of the T_1 wave in the latter conditions. The various changes in the auricular

complex—such as increase in height, width and notching, which were found by Berliner and Master [6] in 61 of 69 cases of mitral stenosis—will also be of assistance.

Disease of the tricuspid valve, which is so frequently associated with preponderance of the right ventricle, characteristically produces inversion of the T wave in lead III but not in lead I.[7] Inversion of the T wave in lead I is a rare finding in cases of mitral stenosis except in association with aortic valvulitis. Disease of the aortic valve is certainly one of the more common causes of preponderance of the left ventricle.

Cases of congenital dextrocardia will not be confused with those of ventricular aneurysm when it is observed that the P wave is inverted in the first lead of the electrocardiogram. This finding will also prevent false interpretation from misplacement of the arm electrodes.

Block of the right bundle branch was not found in any of the cases studied, but it should not be confused with conditions suggesting ventricular aneurysm because of the upright T wave in lead I and the usual alterations in the ventricular complex found in cases of bundle branch block.

The $S_{2,3}$ type showing left axis deviation is not necessarily peculiar to cardiac aneurysm. It has been observed in cases of nonsacculated myocardial infarctions as well as in cases of dilated hearts and those presenting marked enlargement of the left ventricle from other causes. It does, however, occur sufficiently often with cardiac aneurysm to warrant consideration of this condition when it is found.

The occurrence of two divergent types of electrocardiogram, one showing left and the other right axis deviation, is hard to explain. It is especially difficult to rationalize, since the anatomic changes are the same in each group. Pathologic examination was made by the usual methods, although detailed examination for incomplete bundle branch block was not performed. In each of the two groups of cases described, as well as in those presenting evidence of lesions of a bundle branch or other equivocal records, apical aneurysms were observed, as were also sacculations of the left ventricle several centimeters superior to the apexes. In over 80 per cent of cases, the aneurysm occurred in that portion of the heart supplied by the anterior descending branch of the left coronary artery. In each of the four groups noted in the table there were instances of such lesions. We have been unable to establish any

6. Berliner, K., and Master, A. M.: Mitral Stenosis: A Correlation of Electrocardiographic and Pathologic Observations, Arch. Int. Med. **61**:39 (Jan.) 1938.

7. Master, A. M.: Right Ventricular Preponderance of the Heart, Am. J. M. Sc. **186**:714, 1935.

correlation between the location of aneurysm of the left ventricle and the axis deviation produced on the electrocardiogram.

The type of electrical axis of the heart in the $S_{2,3}$ group is not surprising and can be explained by any of the causes more generally accepted as producing axis deviation, namely, the position of the center of gravity of the heart, the weight of the myocardial mass, the length of the fibers or the distance that the impulses traverse through the conduction system. It has been observed by Bohning and Katz [8] that, although preponderance of the left ventricle is most likely to occur with posterior infarction, atypical forms can occur with slow occlusion or with a recent thrombosis superimposed on an older one. It appears from study of the cases in this series that the acuteness of the infarction may be a factor in the causation of the S_1 but not of the $S_{2,3}$ type of electrocardiogram.

By pathologic examination of specimens, it becomes evident that the predominant cardiac mass is the left ventricle. Why this produces an electrical axis deviation usually associated with preponderance of the right ventricle cannot be explained by the older theories of electrical axis deviation. It is paradoxic that the Einthoven equilateral triangle reveals marked right axis deviation with normal ventricular complexes in the presence of enlargement of the left ventricle, yet this fact can apparently be explained by consideration of the relative conducting abilities of the various tissues and fluids involved, as has been shown by Katz and Korey.[9] These authors demonstrated that blood as an electrical conductor is far inferior to cardiac muscle. It would therefore seem that in contradistinction to the intact wall of the right ventricle, the aneurysmal sac and contained thrombus of the left ventricle may relatively detract from rather than add to the electrical forces.

Not in accord with this explanation is case 3, in which aneurysm of the left ventricle containing a thrombus was present. The wall of the sac was devoid of muscular elements, being composed solely of fibrous tissue. The electrocardiogram in this case revealed marked left axis deviation.

The effects of noncardiac organs which play a role in the distribution of the electrical currents away from the heart itself is not known in such instances as those described. It is probable that variations in the conductivity of the particular tissue in contact with the heart [10] or the

8. Bohning, A., and Katz, L. N.: Four Lead Electrocardiogram in Cases of Recent Coronary Occlusions, Arch. Int. Med. **61**:241 (Feb.) 1938.

9. Katz, L. N., and Korey, H.: The Manner in Which the Electrical Currents Generated by the Heart Are Conducted Away, Am. J. Physiol. **111**:83, 1935.

10. Katz, L. N.; Gutman, I., and Ocko, F. H.: Alterations in the Electrical Field Produced by Changes in the Contacts of the Heart with the Body, Am. J. Physiol. **116**:302, 1936.

aneurysm occur. This could possibly explain the differences in the electrocardiograms obtained in the presence of apparently identical lesions. The actual effect of extracardiac transmission of electrical currents cannot be definitely determined at the present time.

Another possible factor causing right axis deviation recordings to be obtained in hearts with left-sided preponderance is the interaction of the rotation of the heart on its anteroposterior axis with that on its longitudinal axis.[11] Figure 2 shows the effect on the electrocardiogram of changing the patient from the supine to each lateral position in a case of aneurysm of the left ventricle. It will be observed that the shift of the axis is not of great magnitude. The shift to the right that occurred in case 3 when the patient was placed in the right lateral position, although definite, does not approach that observed in the S_1 type of electrocardiograms taken of patients in the recumbent position. Obviously, simple alteration of the position of the patient will not reveal the respective magnitude of rotation of the heart on its anteroposterior or longitudinal axis. Other methods that have been used experimentally are unfortunately not clinically applicable.

The problem of explaining which cardiac aneurysms will produce the S_1 type and which will show the $S_{2,3}$ type of cardiogram, is not solved as yet. However, the empiric observation that in 63.7 per cent of all cases the electrocardiograms fall into one of two distinct groups, appears to us to be a significant diagnostic point.

SUMMARY

There is an electrocardiographic syndrome, occurring in 27.3 per cent of cases of aneurysm of the left ventricle following occlusion of the coronary artery, which may be considered to be a presumptive sign of this lesion. It consists of a downward directed major deflection in lead I, with inversion of the T wave and an upright P wave. The ventricular complex in lead III is upright.

Another type, occurring in 36.4 per cent of cases, presents ventricular complexes directed downward in leads II and III with an upright major deflection in lead I that may or may not be of low amplitude.

In 18.2 per cent of cases of cardiac aneurysm, the electrocardiogram shows left bundle branch block, and there were a like number of various other equivocal records, which, although consistent with disease of the coronary artery, were not of diagnostic significance.

11. Meek, W. J., and Wilson, A.: The Effect of Changes in the Position of the Heart on the QRS Complex of the Electrocardiogram, Arch. Int. Med. **36**:614 (Nov.) 1925. Kountz, W. B.; Prinzmetal, M.; Pearson, E. F., and Koenig, K. F.: The Effect of Position of the Heart on the Electrocardiogram: Electrocardiogram in Revived Perfused Human Hearts in the Normal Position, Am. Heart J. **10**:605, 1935.

Roentgen examination, especially roentgenkymography, would seem to be the most reliable means of corroboration of the diagnosis of ventricular aneurysm and should be performed when one or the other of the two types of cardiogram observed in 63.7 per cent of all cases is obtained.

No correlation between the location of the aneurysm and the specific type of electrocardiogram obtained has been established.

The use of the Einthoven equilateral triangle is a convenient means of visualizing deviation of the axis. However, other more recent theories must be considered in order to explain the two divergent types of cardiogram obtained with pathologically identical lesions.

EFFECTS ON THE CARDIOVASCULAR SYSTEM OF MAN OF FLUIDS ADMINISTERED INTRAVENOUSLY

III. STUDIES OF THE GLOMERULAR FILTRATION RATE AS MEASURED BY THE UREA CLEARANCE

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Studies of the effects of the administration intravenously of isotonic and slightly hypertonic solutions of crystalloids on the blood volume and on the dynamics of the circulation in normal man have been reported recently from this laboratory.[1] After such injections there were noted increased blood volume, with decreased hematocrit reading and plasma protein concentration, increased cardiac output and velocity of blood flow, widening of pulse pressure and transient increase in venous pressure.

In the present investigation the effect of the administration intravenously of isotonic solutions of sodium chloride on renal function in normal man has been studied. The changes which occur in the systemic circulation after this procedure, if shared directly by the glomerular capillary circulation, should affect the glomerular filtration rate, according to the filtration-reabsorption theory of renal function. According to this theory, the glomerular filtration rate is determined by the total functioning glomerular capillary surface, the effective filtration pressure in the glomerular capillaries and the rate of renal blood flow. The increase in blood volume, the lowering of plasma protein concentration and the increase in cardiac output which occur after the intravenous injection of

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1. (*a*) Gilligan, D. R.; Altschule, M. D., and Volk, M. C.: The Effects on the Cardiovascular System of Fluids Administered Intravenously in Man: I. Studies of the Amount and Duration of Changes in Blood Volume, J. Clin. Investigation **17**:7, 1938. (*b*) Altschule, M. D., and Gilligan, D. R.: The Effects on the Cardiovascular System of Fluids Administered Intravenously in Man: II. The Dynamics of the Circulation, ibid. **17**:401, 1938.

fluids would be expected, therefore, so to alter these factors associated with renal function as to increase glomerular filtration, unless specific adjustments in the renal vascular dynamics intervene.

MATERIAL AND METHODS

Volumes of 1,000 or 1,500 cc. of physiologic solution of sodium chloride were given intravenously at rates of from 28 to 125 cc. per minute to 8 adult subjects with normal renal and cardiovascular functions. For convenience, the urea clearance was utilized as a measure of relative glomerular filtration rate. The urea clearance was determined for two periods of approximately one hour each before the injection of fluids, during the injection and for two or three periods embracing the first three hours after injection. The arterial and venous blood pressure, pulse rate, concentration of serum protein and hematocrit value were measured before and immediately after administration of the fluid. The extent of change in blood volume was estimated. The methods utilized in these measurements, with the exception of the urea clearance, were outlined in our earlier studies;[1] the change in blood volume was calculated from the changes in protein concentration and hematocrit value, as described in method A of our previous communication.[1a] Urea clearance was measured according to the method of Van Slyke, Page, Hiller and Kirk.[2] Both maximum and standard clearances were calculated in percentages of the mean normal, the values thus being made directly comparable. "Urea plus ammonia" nitrogen was measured by the urease method and by aeration. For calculation of the clearance the volume of urine was corrected for body weight.[3] Specimens of urine were obtained from an inlying catheter in 4 subjects. A light breakfast without tea or coffee was given at 7 a. m., and a light lunch was given to 5 of the patients at 1 p. m. Subjects were requested to drink a glass of water each hour during the control periods so as to insure sufficient output of urine for reliable clearance tests. Specimens of urine were collected from approximately 9 a. m. to 3 p. m.

Because the fluid injected intravenously diluted the plasma, samples of blood for measurement of the urea in the serum were taken before the injection, immediately after the injection and again at the end of either the first or the second period after injection. The urea concentration of the serum taken prior to injection was utilized in the calculation of the urea clearances used as controls. The average of the values before injection and those at the end of injection was used for the calculation of the clearance during the period of injection. Similarly, for the period following injection the average of the values for serum obtained at the beginning and at the end of the period was used in the instances in which the blood urea was measured at the end of this period; in these cases this last value for serum was used for the next two periods. In those instances in which the serum urea was measured at the end of the second period after injection, the values for the first and second periods after injection were calculated by interpolation from the latter

2. Van Slyke, D. D.; Page, I. H.; Hiller, A., and Kirk, E.: Studies of Urea Excretion: IX. Comparison of Urea Clearances Calculated from the Excretion of Urea, of Urea Plus Ammonia, and of Nitrogen Determinable by Hypobromite, J. Clin. Investigation **14**:901, 1935.

3. McIntosh, J. F.; Möller, E., and Van Slyke, D. D.: Studies of Urea Excretion: III. The Influence of Body Size on Urea Output, J. Clin. Investigation **6**:467, 1928.

Data on the Effect of the Intravenous Injection of Physiologic Solution of Sodium Chloride on the Urea Clearance and Certain Aspects of the Circulation of Adults with Normal Cardiac and Renal Functions

Case, Sex, Age, Yr.	Injection of Solution of NaCl: Amount, Cc.	Injection of Solution of NaCl: Rate, Cc. per Min.	Period, Min.	Serum Urea Nitrogen,* Mg. per 100 Cc.	Urine Volume, Cc. per Min.	Urea Clearance, Percentage of Normal	Hematocrit† Reading	Serum Protein, Gm. per 100 Cc.	Calculated Increase in Blood Volume, Cc.	Venous Pressure, Cm. H_2O
1			0-55	....	2.49	126				
F			120	11.9	4.55	99				
30	1,000	28	**162**‡	11.0	1.59	100	....	....	...	....
			212	9.9	2.00	101				
			281	....	1.09	116				
			331	....	5.00	166				
2			0-60	....	0.52	100				
M			120	9.0	2.72	101	30.5	6.52	...	2.6
46	1,000	29	**154**	7.0	3.32	141	27.8	5.86	320	4.4
			234	....	4.94	129				
			354	6.8	5.88	113				
3			0-60	....	0.57	104				
F			152	23.2	0.65	117	38.2	6.86	...	5.9
44	1,000	32	**208**	22.0	1.46	107	32.2	5.81	320	10.1
			326	18.4	1.98	112				
			396	....	1.06	103				
4			0-90	....	0.41	172				
F			194	11.9	0.52	177	....	7.26	...	5.4
42	1,000	33	**235**	10.5	3.81	161	....	6.62	250§	8.4
			310	....	2.64	99				
			369	9.4	0.74	130				
			429	....	0.75	173				
5			0-58	....	1.71	108				
M			170	13.9	9.97	115	44.9	6.98		
37	1,000	35	**211**	13.8	7.00	109	40.8	6.43	60	5.4
			264	....	4.17	94	....	....	...	5.3
			326	13.6	2.94	101				
			404	....	1.80	89				
6			0-59	....	8.05	108				
M			117	6.3	7.33	115	41.5	7.37	...	7.0
32	1,500	82	**162**	4.6	4.27	107	34.7	5.45	970	14.7
			220	5.3	6.04	176				
			282	...	1.81	106				
			342	...	1.43	135				
7			60	...	0.43	131				
M			129	8.8	1.46	110	41.8	6.80	...	5.8
28	1,500	83	**166**	7.5	1.59	98	34.0	4.97	900	11.8
			223	7.5	0.89	134				
			356	...	3.11	118				
8			0-63	....	9.13	78				
M			117	13.2	7.04	73	49.5	8.09	...	7.6
34	1,500	125	**180**	11.1	2.86	68	39.5	5.95	730	12.0
			226	10.6	5.66	84				
			351	....	5.45	74				

* The values given are those obtained at the end of the period; for the method used in estimation of mean values for calculating clearance in any given period, see section on "Methods."

† In each instance the figures for hematocrit readings, serum protein and venous pressure represent values obtained just before and immediately after injection.

‡ The period which has been designated with boldface figures in each case is the one during which fluid was injected; the value for serum urea in this line is that obtained at the end of injection.

§ Plasma volume increase, calculated by assuming the initial hematocrit value to be 40 per cent.

value and the one obtained at the end of injection; the value at the end of the second period after injection was used for the calculation of the clearance in the last period.

RESULTS

The concentration of serum protein and the hematocrit value decreased after the injection of fluids in all of the 7 cases in which these measurements were made. The decreases in protein concentration were approximately 25 per cent in the 3 instances in which 1,500 cc. of fluid was given at rates of from 82 to 125 cc. per minute (table). The calculated blood volume showed increases varying from 60 to 970 cc., the larger increases occurring in cases in which the larger volumes of fluid were injected at the faster rates (table). The pulse rate and the arterial blood pressure were not significantly altered. The venous pressure increased during injection in 6 of 7 studies, the average increase being 4 cm. of water and the greatest increase 8 cm. (case 6; table). These results accord with our earlier observations.[1]

The values for urea clearance obtained during the period of injection of fluids and during the one hour period after the end of injection showed no consistent changes from those obtained during control periods. In 1 instance (case 2) the clearance during the period of injection was 40 per cent higher than that in the control periods; during the first period after the injection the clearance was 40 per cent lower than the average control value in 1 instance (case 4) and 60 per cent higher in another instance (case 6). Similarly, there were no consistent changes in clearance during the later periods of study; in 1 of the 8 studies, the clearance value for a later period was considerably higher (case 1) than the average control value.

COMMENT

Peters[4] reviewed the evidences that the area of the glomerular filtering surface, the renal blood flow, the osmotic pressure of the plasma proteins and the glomerular capillary pressure are important factors in determining the glomerular filtration rate, according to the filtration-reabsorption theory of renal function. Since the intravenous injection of fluids as carried out in the present studies induces increased blood volume, increased cardiac output and lowering of the concentration of the plasma proteins (table),[1] this procedure should increase glomerular filtration, unless specific changes in the renal circulatory system intervene.

Our studies demonstrate no effect on the urea clearance of the combination of changes in systemic circulation occurring after the injection of isotonic solutions of sodium chloride intravenously. The occasional high or low results obtained in a single one hour period during or after

4. Peters, J. P.: Body Water: The Exchange of Fluids in Man, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

the end of injection in a few of the experiments (table) are interpreted as not significant with respect to the injection of fluid; similar results have been obtained by others who have studied the normal variations in urea clearance during several successive one hour periods. It is to be noted that the increases in blood volume and decreases in plasma protein concentration were pronounced in the subjects receiving 1,500 cc. of fluid at rapid rates (cases 6, 7 and 8; table); it was found in our earlier studies [1a] that after such injections changes in the blood volume and plasma protein were still appreciable up to approximately two hours after the end of injection. Peripheral vasodilatation, as evidenced by flushing of the skin, occurred in a majority of the subjects in the present study. Presumably, increases in cardiac output and velocity of blood flow occurred during the period of injection and during at least a part of the subsequent period of measurement of urea clearance.[1b]

We have utilized the urea clearance test as a relative measure of glomerular filtration rate. Urea is reabsorbed by the tubules so that the amount of blood cleared of urea per minute does not represent an absolute measure of glomerular filtration rate. However, since the maximum urea clearance varies proportionately with the clearances of creatinine, sucrose, inulin and xylose,[5] the test is generally accepted as a relative measure of glomerular filtration rate. Values for the urea clearance as expressed in percentages of the average normal are presented in the table so that standard and maximum clearances are directly comparable.

The absence of increases in glomerular filtration rate with the changes in systemic circulation occurring after the administration of fluids intravenously seems to result from specific adjustments in the renal vascular dynamics, afforded by the peculiar anatomic and vasomotor characteristics of the renal vascular system.

There are numerous other examples in the literature which demonstrate constancy of glomerular filtration rate in spite of changes in systemic circulation. Thus, although the cardiac output and the arterial blood pressure are increased by strenuous muscular exercise, the urea clearance is not increased, and even may be decreased, under such conditions.[6] The glomerular rate is not affected by the injection of

5. Winkler, A. W., and Parra, J.: The Measurement of Glomerular Filtration: Creatinine, Sucrose, and Urea Clearances in Subjects Without Renal Disease, J. Clin. Investigation **16**:859, 1937. Shannon, J. A., and Smith, H. W.: The Excretion of Inulin, Xylose and Urea by Normal and Phlorizinized Man, ibid. **14**: 393, 1935. Van Slyke and others.[2]

6. MacKay, E. M.: Studies of Urea Excretion: V. The Diurnal Variation of Urea Excretion in Normal Individuals and Patients with Bright's Disease, J. Clin. Investigation **6**:505, 1928. Van Slyke, D. D.; Alving, A., and Rose, W. C.: Studies of Urea Excretion: VII. The Effects of Posture and Exercise on Urea Excretion, ibid. **11**:1053, 1932.

epinephrine.[7] The glomerular filtration rate is not increased in patients with high blood pressure due to essential hypertension,[8] nor does it decrease when the arterial blood pressure decreases either spontaneously or after unilateral renal denervation.[9] Either no change or a slight decrease in glomerular filtration rate has been observed when peripheral vasodilatation and decrease in arterial blood pressure are brought about by the administration of sodium nitrite to normal subjects and patients with primary hypertension.[10] The glomerular filtration rate is not increased in artificially induced hyperpyrexia, with its accompanying increased cardiac output.[11] Normal glomerular filtration obtains in patients with hypoproteinemia due to protein malnutrition or to the nephrotic state.[4]

Decreased glomerular filtration is found, on the other hand, in the presence of shock,[4] when the blood pressure is lowered during spinal anesthesia,[12] and in oliguria due to dehydration.[13] Effective treatment of such conditions with intravenous injections of fluids undoubtedly results in increased glomerular filtration rate. It appears that the renal circulation in man can so adjust itself as to maintain relative constancy of glomerular filtration, except under conditions of extreme demand on the systemic circulatory system.

Keutmann and Bassett[14] reported an increase in urea clearance in a nephritic patient on the day after a transfusion of 800 cc. of plasma; they suggested that the increased glomerular filtration rate resulted from increased plasma volume. In an unreported study, we noted no change in urea clearance after the transfusion of 500 cc. of blood in a nephritic patient with a urea clearance of 5 per cent of normal; in the case of another nephritic patient, with a control clearance of 4 per

7. Chasis, H.; Ranges, H. A.; Goldring, W., and Smith, H. W.: The Control of Renal Blood Flow and Glomerular Filtration in Normal Man, J. Clin. Investigation **17**:683, 1938.

8. Roelsen, E.: Determination of the Permeability of Tissues to Creatinine by the Holten and Rehberg Method in Hypertension, Hospitalstid. **75**:579, 1932.

9. Page, I. H.: The Effect on Renal Efficiency of Lowering Arterial Blood Pressure in Cases of Essential Hypertension and Nephritis, J. Clin. Investigation **13**:909, 1934.

10. Weiss, S., and Ellis, L. B.: Influence of Sodium Nitrite on the Cardiovascular System and on Renal Activity in Health, in Arterial Hypertension and in Renal Disease, Arch. Int. Med. **52**:105 (July) 1933.

11. Farr, L. E., and Moen, J. K.: Effect of Induced Hyperpyrexia on the Urea Clearance of Rheumatic Patients, Am. J. M. Sc. **197**:53, 1939. Chasis and others.[7]

12. Lassen, H. C. A., and Husfeldt, E.: Kidney Function and Blood Pressure, J. Clin. Investigation **13**:263, 1934.

13. Chesley, L. C.: Renal Excretion at Low Urine Volumes and the Mechanism of Oliguria, J. Clin. Investigation **17**:591, 1938.

14. Keutmann, E. H., and Bassett, S. H.: Studies on the Mechanism of Proteinuria, J. Clin. Investigation **16**:767, 1937.

cent of normal, 1,000 cc. of physiologic solution of sodium chloride administered intravenously at the rate of 28 cc. per minute did not affect the urea clearance.

Medes and Herrick [15] observed a parallelism between renal blood flow, as measured by the thermostromuhr, and creatinine clearance in the dog. Van Slyke and his associates,[16] using the method of explanting the kidney, also demonstrated that in the dog spontaneous variations in urea clearance parallel chiefly variations in renal blood flow. Chasis and his co-workers [7] measured clearances of diodrast, phenolsulfonphthalein and inulin simultaneously in man to obtain information on the effect on the glomerular filtration rate of changes in renal blood flow brought about by certain drugs. If it is correct to assume that the diodrast clearance is an exact [17] or proportional measurement of renal blood flow, the results of these authors indicate that the glomerular filtration rate in man may not be affected by changes in renal blood flow.[7] These authors pointed out that this may obtain, since effective glomerular capillary pressure and effective glomerular filtering surface are affected by the state of both the afferent and the efferent arterioles of the kidney.

Schmitz [18] studied the glomerular filtration rate, as measured by the creatinine clearance, after the intravenous injection of physiologic solution of sodium chloride in dogs. In contrast to our results in man, he found large increases in clearances in the dog. The findings of Chasis and his co-workers [7] indicate that in man the glomerular filtration rate does not vary directly, within certain limits, with renal blood flow, whereas other investigators have found that in the dog the filtration rate does vary with renal blood flow. Van Slyke and his associates [16] pointed out that the variations in urea clearance produced by alterations in diet and other changes are much greater in the dog than in man. The difference between the results of Schmitz after the

15. Medes, G., and Herrick, J. F.: Blood Flow to the Kidney and Creatinine Clearance, Proc. Soc. Exper. Biol. & Med. **31**:116, 1933.

16. Van Slyke, D. D.; Rhoads, C. P.; Hiller, A., and Alving, A. S.: Relationships Between Urea Excretion, Renal Blood Flow, Renal Oxygen Consumption, and Diuresis: The Mechanism of Urea Excretion, Am. J. Physiol. **109**:336, 1934.

17. The average effective renal blood flow of 775 cc. per square meter of body surface per minute obtained by these authors for normal man at rest appears too great, being approximately 35 per cent of the total output of the left ventricle with the subject at rest. Calculations from the data of E. K. Marshall Jr. (Studies on the Cardiac Output of the Dog: I. The Cardiac Output of the Normal Unanesthetized Dog, Am. J. Physiol. **77**:459, 1926) on the cardiac output of the unanesthetized nonpregnant dog and of Van Slyke and his associates [16] on the renal blood flow in the dog measured by the method of Fick indicate that for this species the renal blood flow is only 16 per cent of the output of the left ventricle.

18. Schmitz, H. L.: Studies on the Action of Diuretics: I. The Effect of Euphyllin and Salyrgan upon Glomerular Filtration and Tubular Reabsorption, J. Clin. Investigation **11**:1075, 1932.

intravenous administration of fluids in dogs and our results in man may be attributable to differences based on species.

Since no exact regimen of administration of fluids by mouth was invoked in these studies,[19] the nature of the diuresis brought about by the injections of physiologic solution of sodium chloride cannot be described exactly. It is evident, however, that diuresis was not prompt (table). Similarly, the same volume of isotonic solution of sodium chloride when administered orally to normal man is eliminated gradually over a period of several hours, in contrast to prompt elimination of similar volumes of distilled water.[4]

SUMMARY

The effect of the intravenous administration of 1,000 to 1,500 cc. of physiologic solution of sodium chloride on the glomerular filtration rate, as measured relatively by the urea clearance, of adults with normal renal and cardiovascular functions has been studied. The fluids were injected at rates sufficiently rapid to cause increases in blood volume and cardiac output, decreases in plasma protein concentration, transitory increases in venous pressure and evidences of peripheral vasodilatation.

The glomerular filtration rate was not changed by the injections of fluid, even in those cases in which great changes in the systemic circulation were shown.

The absence of increase in glomerular filtration in the presence of hypervolemia, increased cardiac output and lowered protein osmotic pressure, as induced in our studies, appears to result from specific adjustments in the renal vascular dynamics. No information is available from our studies as to the nature of such renal adjustments.

These results, together with those obtained by other investigators in certain clinical conditions and after the administration of certain drugs demonstrate that the rate of glomerular filtration may not be affected in the presence of large changes in the systemic circulation.

19. Subjects were requested to drink a glass of water each hour during the control periods, so as to insure sufficient output of urine for reliable clearance tests; the overgenerous cooperation of patients 5, 6 and 8 explains the water diuresis observed in the control periods in these studies.

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

XI. DIETS CONTAINING DRIED EXTRACTED LIVER

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The effect of feeding diets containing varying percentages of dried whole liver to intact, unilaterally nephrectomized and partially nephrectomized rats has been presented.[1] In order to study the effect of removing the water-soluble extracts, dried extracted liver was fed to a similar group of animals. This investigation is concerned with the effect of diets containing increasing amounts of dried extracted liver on the weight of the kidney and of the heart, the blood pressure, the renal function and the relation of the concentration of urea in the blood and that in the urine of intact, unilaterally nephrectomized and partially nephrectomized rats.

EXPERIMENTAL METHODS

White rats, raised in the Laboratory of Physiological Chemistry of the University of Virginia, were maintained on a stock diet until they were between 60 and 70 days old, when unilateral nephrectomy or subtotal nephrectomy was performed. The details of the operative procedure and the care of the animals have been described elsewhere.[1]

Renal function was determined by a modified Addis urea clearance test [2] and was represented by the urea ratio, $\frac{\text{urea excretion per hour}}{\text{urea in 100 cc. of blood}}$. Blood pressure was read by direct cannulation of the carotid artery while the animal was under ether anesthesia. The heart and kidney were weighed immediately after the animal was killed. The surface area was calculated from the weight of the animal by the formula of Lee.[3] The weight of the heart and of the kidney per unit of surface

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1. Chanutin, A.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: III. Diets Containing Whole Dried Liver, Liver Residue and Liver Extract, Arch. Int. Med. **54**:720 (Nov.) 1934.

2. Chanutin, A., and Ludewig, S.: Experimental Insufficiency Produced by Partial Nephrectomy: V. Diets Containing Whole Dried Meat, Arch. Int. Med. **58**:60 (July) 1936.

3. Lee, M. O.: Am. J. Physiol. **89**:24, 1929.

area is expressed by $\frac{\text{H. W.}}{\text{S. A.}}$ and $\frac{\text{K. W.}}{\text{S. A.}}$, respectively. The dried extracted liver was the residue from cold storage hog liver which had been thoroughly extracted with hot water (approximately 90 C.). The animals were fed the experimental diets from seventy to one hundred and seventy-five days. The diets (table 1) are designated EL 10, EL 20, EL 40, EL 60 and EL 80 in accordance with the percentage of dried extracted liver used.

EXPERIMENTAL RESULTS AND ANALYSIS OF OBSERVATIONS

Controls (Intact and Unilaterally Nephrectomized Rats).—The effects of diets on 161 intact and 96 unilaterally nephrectomized rats are shown in table 2, in which are recorded observations of the duration of the experiment, the surface area, the blood pressure, the $\frac{\text{heart weight}}{\text{surface area}}$ ratio, the $\frac{\text{kidney weight}}{\text{surface area}}$ ratio, the total solids of the kidneys, the urea ratio and the $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratio.

TABLE 1.—*Composition of Rations*

Diet	Concentration of Component in Diet, Percentage						
	Dried Extracted Liver	Starch	Lard	Cod Liver Oil	Dried Yeast	Salt Mixture	Nitrogen
EL 10	10	62	14	5	5	4	1.5
EL 20	20	52	14	5	5	4	2.9
EL 40	40	32	14	5	5	4	5.1
EL 60	60	12	14	5	5	4	7.2
EL 80	80	6	..	4	6	4	9.6

Blood Pressure and Heart Weight: It is interesting that only 7 of the 161 intact rats and 3 of the 96 unilaterally nephrectomized rats had blood pressures over 140 mm. of mercury and none above 150 mm. In these few animals the elevation in blood pressure did not appear to be related to the concentration of extracted dried liver in the diet. The $\frac{\text{H. W.}}{\text{S. A.}}$ ratios, as presented in table 2, are fairly constant for all diets, with one exception: The average value of the $\frac{\text{H. W.}}{\text{S. A.}}$ ratio is appreciably lower for the unilaterally nephrectomized rats on the EL 80 diet.

Kidneys: The $\frac{\text{K. W.}}{\text{S. A.}}$ ratios for the intact and the unilaterally nephrectomized rats, except those for the unilaterally nephrectomized rats receiving the EL 80 diet, increase progressively with the increase in the intake of extracted liver. When the $\frac{\text{K. W.}}{\text{S. A.}}$ ratios for the intact and the unilaterally nephrectomized animals receiving the EL 10 diet are expressed as unity, the respective ratios for the animals on the diets from EL 10 to EL 80 are as follows: for the intact animals,

TABLE 2.—*Observations on Control Animals Fed a Variety of Diets*

Heart Weight, Kidney Weight

TABLE 2.—*Observations on Control Animals Fed a Variety of Diets*

Renal Condition and Diet	Value	Duration of Experiment, Days	Surface Area	Blood Pressure, Mm.	Heart Weight: Surface Area × 100, Gm.	Kidney Weight: Surface Area × 100, Gm.	Total Solids of the Kidneys, Percentage	Urea Ratio	Urea Ratio / Kidney Weight
2 kidneys EL 10	Minimum	72	222	106	0.140	0.334	22.3	31	25
	Maximum	161	386	146	0.176	0.490	24.8	66	49
	Average	128 ± 5.8	298 ± 6.3	128	0.162	0.390 ± 0.007	23.4	44 ± 1.9	39 ± 1.4
	Rats	32	32	32	32	32	5	27	27
1 kidney EL 10	Minimum	114	260	116	0.150	0.267	23.4	22	30
	Maximum	121	334	142	0.181	0.361	26.2	40	41
	Average	116 ± 1.9	290 ± 7.1	130	0.168	0.297 ± 0.008	24.9	31 ± 1.8	36 ± 1.2
				128 ± 1.3*	0.168 ± 0.001*				
	Rats	13	13	13	13	13	13	11	11
2 kidneys EL 20	Minimum	78	260	112	0.139	0.348	23.2	37	26
	Maximum	168	428	148	0.183	0.475	25.8	72	50
	Average	132 ± 7.6	342 ± 7.6	126	0.166	0.413 ± 0.009	24.6	55 ± 2.4	38 ± 1.2
	Rats	25	25	25	25	25	6	20	20
1 kidney EL 20	Minimum	99	280	114	0.138	0.236	21.5	32	31
	Maximum	177	406	148	0.181	0.370	26.7	62	53
	Average	135 ± 8.6	356 ± 7.3	128	0.161	0.299 ± 0.007	24.4	46 ± 1.6	43 ± 1.5
				127 ± 1.2*	0.163 ± 0.002*				
	Rats	26	26	26	26	26	18	22	22
2 kidneys EL 40	Minimum	83	276	112	0.148	0.375	23.0	35	25
	Maximum	174	428	140	0.187	0.555	25.4	100	47
	Average	131 ± 6.5	340 ± 8.0	123	0.167	0.450 ± 0.009	24.1	60 ± 3.5	38 ± 1.5
	Rats	25	25	25	25	25	7	21	21
1 kidney EL 40	Minimum	102	278	106	0.148	0.293	22.0	31	33
	Maximum	188	403	126	0.170	0.457	26.6	62	43
	Average	149 ± 12.7	350 ± 12.5	121	0.159	0.376 ± 0.015	25.1	50 ± 4.0	38 ± 1.1
				122 ± 1.3*	0.163 ± 0.002*				
	Rats	11	11	11	11	11	8	9	9
2 kidneys EL 60	Minimum	80	286	108	0.141	0.421	21.7	41	30
	Maximum	174	426	144	0.199	0.655	24.7	101	49
	Average	148 ± 6.0	342 ± 6.8	123	0.166	0.520 ± 0.011	22.9	68 ± 2.7	38 ± 1.0
	Rats	37	37	37	37	37	11	30	30
1 kidney EL 60	Minimum	110	278	112	0.126	0.354	22.9	32	24
	Maximum	126	392	144	0.184	0.502	26.1	66	45
	Average	114 ± 1.4	338 ± 6.8	126	0.161	0.411 ± 0.010	25.0	48 ± 1.8	36 ± 1 6
				124 ± 1.2*	0.163 ± 0.002*				
	Rats	23	23	23	23	23	21	21	14
2 kidneys EL 80	Minimum	85	252	110	0.131	0.430	22.3	34	24
	Maximum	166	398	146	0.194	0.635	26.2	92	44
	Average	129 ± 4.8	324 ± 6.4	123	0.157	0.535 ± 0.009	24.4	58 ± 2.5	33 ± 0.8
	Rats	43	43	42	43	43	19	37	37
1 kidney EL 80	Minimum	97	268	110	0.134	0.324	22.9	32	20
	Maximum	120	376	138	0.178	0.454	24.8	75	52
	Average	108 ± 2.2	312 ± 7.8	120	0.147	0.386 ± 0.008	23.9	46 ± 2.4	39 ± 1.5
				122 ± 1.1*	0.153 ± 0.002*				
	Rats	22	22	21	22	22	11	21	21

* Average and standard error for control animals on a specific diet.

1, 1.06, 1.15, 1.33 and 1.37; for the unilaterally nephrectomized animals, 1, 1.0, 1.26, 1.38 and 1.30. A similar comparison of the total solids of the kidneys gives practically the same result.

TABLE 3.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 10 per Cent Dried Extracted Liver*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight: Surface Area, × 100	Kidney Weight: Surface Area, × 100	Total Solids of the Kidneys, Percentage	Urea Ratio
1	97	252	130	0.158	0.215	....	12
2	97	274	134	0.196	0.287	....	18
3	97	231	186	0.254	0.175	....	4
4	97	244	158	0.215	0.240	....	8
5	97	341	132	0.174	0.186	....	19
6	97	265	144	0.181	0.176	....	..
7	97	248	136	0.180	0.165	....	8
8	97	340	128	0.181	0.188	....	..
9	97	240	130	0.161	0.175	....	13
10	97	262	132	0.171	0.166	....	8
11	97	280	128	0.173	0.174	....	..
12	122	256	142	0.177	0.162	25.8	13
13	124	275	136	0.188	0.232	22.7	19
14	124	280	230	0.253	0.228	17.5	..
15	124	238	116	0.168	0.182	23.2	7
16	125	297	162	0.173	0.261	....	11
17	125	265	146	0.167	0.149	....	6
18	125	283	198	0.197	0.376	....	8
19	125	258	158	0.171	0.284	....	11
20	125	230	168	0.166	0.174	....	13
21	125	265	152	0.179	0.196	....	12
22	125	274	166	0.182	0.302	....	..
23	125	348	154	0.190	0.219	....	..
24	125	266	136	0.160	0.200	....	..
25	125	380	124	0.197	0.246	24.0	22
26	125	308	144	0.202	0.187	22.0	10
27	125	289	156	0.197	0.244	21.7	9
28	125	242	228	0.250	0.232	....	5
29	125	258	126	0.178	.....	....	14
30	127	334	126	0.200	0.192	....	13
31	127	383	134	0.192	0.266	....	10
32	127	248	130	0.168	0.170	....	15
33	127	205	176	0.164	0.168	....	7
34	127	314	132	0.172	0.197	....	22
35	127	232	138	0.165	0.160	....	9
36	127	220	132	0.151	0.174	....	5
37	127	328	250	0.235	0.231	....	7
38	127	295	198	0.197	0.422	....	..
39	127	302	134	0.179	0.233	....	..
40	127	324	128	0.188	0.222	....	10
41	140	265	160	0.195	0.219	....	6
42	152	333	182	0.201	0.323	....	10
43	152	250	118	0.161	0.225	....	..
44	152	301	152	0.222	0.231	....	8
45	152	274	134	0.174	0.274	....	19

Urea Ratios: The average urea ratios for the animals with intact kidneys receiving the EL 10, the EL 20, the EL 40, the EL 60 and the EL 80 diet are 44, 55, 60, 68 and 58, respectively. There is a significant progressive increase in the values, followed by a marked decrease for the animals receiving the EL 80 diet. The average values

for the unilaterally nephrectomized animals are 31, 46, 50, 48 and 46, respectively. The ratio for the animals receiving the EL 10 diet is the only low value obtained, while the remaining ratios are fairly constant regardless of diet.

TABLE 4.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 20 per Cent Dried Extracted Liver*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight: Surface Area, × 100	Kidney Weight: Surface Area, × 100	Total Solids of the Kidneys, Percentage	Urea Ratio
1	124	355	122	0.181	0.265	20.3	7
2	124	285	164	0.167	0.376	17.7	16
3	124	354	138	0.166	0.238	22.0	9
4	124	307	126	0.176	0.304	19.2	18
5	124	340	168	0.189	0.248	20.4	16
6	126	379	130	0.178	0.323	17.1	12
7	126	374	208	0.243	0.367	14.3	5
8	126	285	198	0.280	0.264	16.1	3
9	126	408	166	0.189	0.313	18.6	17
10	126	380	142	0.197	0.371	18.9	15
11	131	354	128	0.181	0.244	....	12
12	131	328	176	0.197	0.268	....	21
13	132	370	158	0.179	0.297	....	12
14	132	374	182	0.189	0.266	....	16
15	132	396	144	0.213	0.290	....	8
16	133	362	120	0.164	0.238	....	25
17	133	320	162	0.191	0.262	....	19
18	133	302	132	0.173	0.314	....	16
19	133	302	170	0.187	0.256	....	14
20	133	302	224	0.253	0.212	....	14
21	133	379	160	0.220	0.202	....	8
22	133	427	154	0.183	0.272	....	29
23	133	270	166	0.190	0.270	....	..
24	133	341	194	0.206	.....	....	..
25	133	372	202	0.232	0.350	....	..
26	133	346	136	0.171	0.218	....	29
27	146	306	162	0.233	0.462	....	..
28	146	366	132	0.181	0.266	....	18
29	150	380	186	0.259	0.362	....	7
30	150	310	154	0.195	0.242	....	3
31	150	289	170	0.248	0.390	....	9
32	150	314	182	0.293	0.206	....	5
33	150	322	146	0.242	0.480	....	22
34	150	374	166	0.196	0.334	....	4
35	154	291	146	0.191	0.358	....	..
36	154	278	194	0.228	0.232	....	8
37	154	345	148	0.177	0.394	....	7
38	154	380	146	0.182	0.374	....	11
39	154	289	164	0.193	0.474	....	7
40	154	350	158	0.180	0.306	....	17
41	154	360	148	0.193	0.264	....	..

The $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratios are 39, 38, 38, 38 and 33 for the intact rats receiving the EL 10, the EL 20, the EL 40, the EL 60 and the EL 80 diet, respectively; for the unilaterally nephrectomized rats the ratios are 36, 43, 38, 36 and 39, respectively. Despite the wide variations in diet, it is seen, these ratios are extremely constant for both the intact and the unilaterally nephrectomized rats.

TABLE 5.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 40 per Cent Dried Extracted Liver*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight: Surface Area, × 100	Kidney Weight: Surface Area, × 100	Total Solids of the Kidneys, Percentage	Urea Ratio
1	71	346	126	0.174	0.280	....	19
2	71	256	...	0.148	0.250	....	13
3	71	265	102	0.164	0.445	....	10
4	71	350	132	0.159	0.390	....	20
5	71	280	122	0.151	0.243	....	28
6	71	307	132	0.160	0.273	....	25
7	73	380	148	0.179	0.558	....	10
8	73	291	136	0.200	0.250	....	9
9	73	268	134	0.148	0.286	....	12
10	73	283	136	0.155	0.383	....	12
11	73	292	134	0.137	0.258	....	16
12	101	274	124	0.162	0.465	15.0	10
13	101	341	130	0.171	0.362	13.4	5
14	101	308	142	0.170	0.514	12.6	6
15	103	360	126	0.177	0.298	20.8	17
16	103	308	124	0.166	0.264	20.7	22
17	103	291	178	0.228	0.264	15.1	6
18	103	308	128	0.160	0.231	20.8	..
19	108	374	142	0.179	0.294	21.8	..
20	125	372	164	0.191	0.440	16.3	13
21	125	411	156	0.180	0.322	18.0	20
22	125	334	176	0.228	0.633	10.6	3
23	125	356	130	0.174	0.356	16.7	12
24	125	373	126	0.165	0.318	22.0	28
25	126	291	134	0.155	0.544	14.0	13
26	126	356	144	0.186	0.487	13.2	8
27	126	285	136	0.173	0.348	18.6	13
28	126	320	184	0.232	0.384	13.4	3
29	126	308	132	0.156	0.247	21.6	27
30	126	299	186	0.216	0.504	14.7	10
31	127	379	144	0.199	0.440	16.7	9
32	127	320	150	0.163	0.447	15.7	10
33	127	364	134	0.165	0.410	17.0	15
34	127	386	138	0.210	0.488	14.9	7
35	127	358	172	0.227	0.573	17.6	4
36	127	346	134	0.187	0.446	19.7	..
37	127	374	142	0.195	0.523	14.8	10
38	127	356	192	0.238	0.578	11.7	..
39	132	266	198	0.195	0.450	16.7	..
40	132	283	146	0.172	0.309	18.9	8
41	132	270	162	0.179	0.341	16.9	10
42	132	275	136	0.159	0.290	19.9	..
43	132	285	144	0.159	0.358	16.8	8
44	132	278	136	0.152	0.245	20.8	12
45	132	268	166	0.197	0.261	15.9	..
46	132	299	158	0.159	0.346	15.0	..
47	132	258	214	0.222	0.385	14.0	4
48	132	280	128	0.167	0.350	20.0	9
49	132	302	158	0.184	0.315	18.7	11
50	132	280	162	0.205	0.495	14.0	6
51	134	276	126	0.162	0.305	18.0	6
52	134	343	154	0.250	0.635	12.8	5
53	134	379	140	0.182	0.374	20.8	15
54	134	291	156	0.147	0.452	13.6	..
55	134	268	136	0.158	0.340	13.6	13
56	142	283	138	0.159	0.421	....	..
57	142	275	202	0.207	0.583	....	4
58	142	285	210	0.209	0.312	....	4
59	142	288	196	0.199	0.500	....	8

From table 2 it appears that blood pressures below 140 mm. of mercury and urea ratios above 30 may be accepted as normal for all animals.

TABLE 6.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 60 per Cent Dried Extracted Liver*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight / Surface Area, × 100	Kidney Weight / Surface Area, × 100	Total Solids of the Kidneys, Percentage	Urea Ratio
1	89	314	160	0.230	0.550	14.7	8
2	89	265	190	0.177	0.510	13.5	11
3	89	270	154	0.179	0.508	12.9	5
4	89	306	162	0.183	0.473	12.9	6
5	89	334	140	0.193	0.431	17.4	16
6	89	307	154	0.183	0.455	13.2	..
7	91	256	142	0.181	0.629	....	..
8	91	297	136	0.179	0.513	....	15
9	91	304	158	0.191	0.545	....	6
10	96	324	158	0.232	0.726	....	6
11	98	374	142	0.168	0.622	....	22
12	98	274	142	0.166	0.476	....	12
13	98	248	136	0.202	0.484	....	..
14	98	291	128	0.158	0.481	....	17
15	98	266	134	0.146	0.395	....	17
16	104	256	196	0.228	0.302	13.5	3
17	104	256	162	0.223	0.362	12.6	3
18	104	289	158	0.205	0.458	17.8	9
19	104	262	134	0.175	0.295	18.8	13
20	106	334	142	0.220	0.650	13.0	9
21	106	289	152	0.180	0.331	18.6	15
22	106	301	198	0.196	0.450	14.6	9
23	107	336	190	0.199	0.113	....	9
24	107	307	170	0.180	0.604	....	29
25	107	283	122	0.151	0.372	....	28
26	109	313	152	0.176	0.642	12.8	..
27	109	244	200	0.205	0.620	11.7	5
28	109	283	148	0.186	0.534	15.7	14
29	109	260	166	0.196	0.633	15.0	15
30	109	266	198	0.186	0.546	13.8	10
31	113	297	148	0.185	0.442	16.8	11
32	113	278	176	0.180	0.538	13.6	7
33	113	316	172	0.174	0.471	17.4	7
34	113	286	168	0.210	0.376	13.8	19
35	126	260	144	0.186	0.770	12.7	10
36	126	274	138	0.164	0.491	16.5	..
37	126	285	136	0.168	0.740	14.0	18
38	146	270	146	0.141	0.388	....	10
39	146	295	136	0.155	0.417	....	17
40	146	310	146	0.183	0.730	....	7
41	146	270	124	0.151	0.390	....	15
42	146	295	128	0.157	0.308	....	22
43	148	270	144	0.135	0.454	....	12
44	148	244	122	0.151	0.293	....	10
45	148	308	156	0.164	0.854	....	10
46	148	246	130	0.200	0.686	....	3

Partially Nephrectomized Rats.—The duration of the experiment, the surface area, the blood pressure, the $\frac{\text{H. W.}}{\text{S. A.}}$ ratio, the $\frac{\text{K. W.}}{\text{S. A.}}$ ratio, the total solids of the kidney and the urea ratio for partially nephrectomized rats receiving the EL 10, the EL 20, the EL 40, the EL 60 and the EL 80 diets are shown in detail in tables 3 to 7.

Charts 1 to 5 were prepared from these tables to facilitate comparison of the effects of the different diets on the blood pressure, $\frac{K.\ W.}{S.\ A.}$ ratio, the urea ratio and the relation between the concentration of urea in the blood and in the urine.

Blood Pressure: The data on blood pressure are summarized in chart 1. The group receiving the EL 20 diet had the greatest percentage

TABLE 7.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 80 per Cent Dried Extracted Liver*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight: Surface Area, × 100	Kidney Weight: Surface Area, × 100	Total Solids of the Kidneys, Percentage	Urea Ratio
1	82	232	152	0.172	0.361	....	12
2	86	280	140	0.153	0.438	....	17
3	89	254	144	0.158	0.478	....	18
4	89	248	146	0.165	0.529	....	..
5	96	248	118	0.154	0.433	....	17
6	96	246	132	0.163	0.661	....	15
7	96	292	156	0.167	0.838	....	14
8	100	289	142	0.155	0.475	21.1	18
9	101	274	152	0.177	0.685	12.3	10
10	101	278	206	0.192	0.781	11.6	12
11	101	323	164	0.177	0.623	11.6	14
12	101	348	152	0.172	0.596	17.9	21
13	106	234	156	0.160	0.410	....	13
14	106	272	152	0.187	0.534	14.8	8
15	106	270	174	0.202	0.740	12.9	16
16	106	242	...	0.195	0.526	14.9	11
17	107	316	136	0.170	0.415	....	24
18	107	320	...	0.171	0.447	....	24
19	107	297	138	0.161	0.446	....	10
20	107	256	148	0.153	0.330	....	18
21	109	274	136	0.148	0.348	19.7	20
22	117	260	130	0.161	0.353	....	15
23	117	258	124	0.162	0.696	....	20
24	122	304	130	0.170	0.456	17.7	17
25	122	313	134	0.174	0.577	17.0	29
26	122	222	126	0.150	0.408	17.1	11
27	122	304	144	0.169	0.511	18.0	24
28	138	289	134	0.145	0.655	13.9	11
29	138	278	134	0.162	0.717	13.9	7
30	138	275	172	0.146	0.510	19.6	22
31	138	254	134	0.150	0.476	16.2	13
32	138	286	156	0.175	0.606	13.4	8
33	138	232	122	0.178	0.480	13.2	4

of animals with pressures above 160 and above 180 mm. of mercury, and the group receiving the EL 80 diet had the smallest percentage of hypertensive animals. In order to determine the effect of diet on the incidence of unusually high pressures, the percentage of rats with blood pressures above 200 mm. in the group receiving each diet was listed as follows: EL 10, 16; EL 20, 22; EL 40, 14; EL 60, 13, and EL 80, 3. The highest individual blood pressure, 250 mm., was noted in an animal receiving the EL 10 diet.

A positive relation between the height of blood pressure and the degree of cardiac hypertrophy has been demonstrated [4] by calculating the coefficient of correlation between the blood pressure and the $\frac{\text{H. W.}}{\text{S. A.}}$ ratio. In the present study the coefficients with their probable errors, listed according to the diet, are as follows: EL 10, 0.76 ± 0.04; EL 20, 0.49 ± 0.08; EL 40, 0.59 ± 0.06; EL 60, 0.44 ± 0.08, and EL 80, 0.49 ± 0.09. A fairly high degree of correlation was obtained for the animals receiving the EL 10 diet, and a substantial relation was noted for the remaining groups.

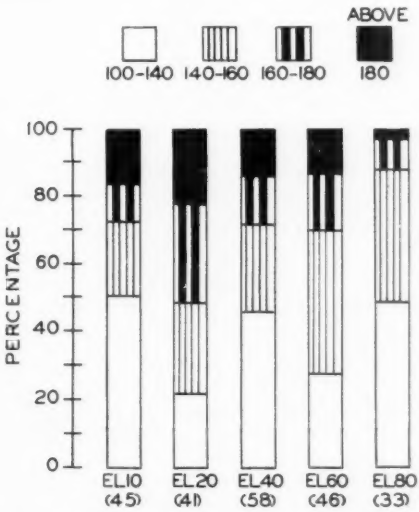

Chart 1.—Effect of diet on the blood pressure of partially nephrectomized rats. The figures in parentheses represent the number of animals.

Kidneys: The data on the total solids of the kidneys per hundred square centimeters of surface area are presented in chart 2. This value is more reliable than the $\frac{\text{K. W.}}{\text{S. A.}}$ ratio, since variations in the water content of the stump of the kidney are eliminated. The average values for the dried kidneys expressed in milligrams with standard errors are 47 ± 2.1, 56 ± 2.3, 64 ± 1.8, 74 ± 3.1 and 85 ± 3.4, for the animals receiving the EL 10, the EL 20, the EL 40, the EL 60 and the EL 80

4. Chanutin, A., and Barksdale, E. E.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: II. Relationship of Left Ventricular Hypertrophy, the Width of the Cardiac Muscle Fiber and Hypertension in the Rat, Arch. Int. Med. **52**:739 (Nov.) 1933.

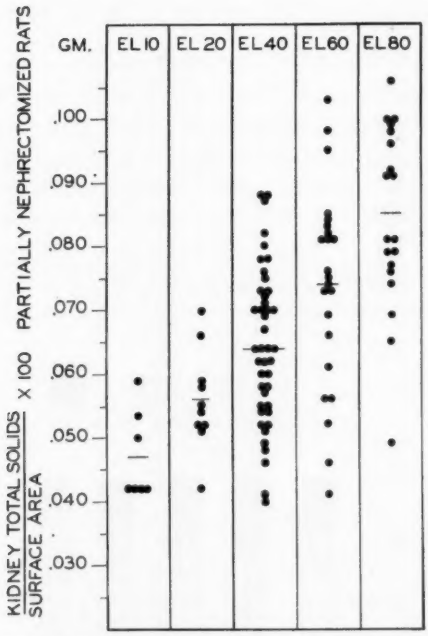

Chart 2.—Effect of diet on the total solids of the kidneys per hundred square centimeters of surface area.

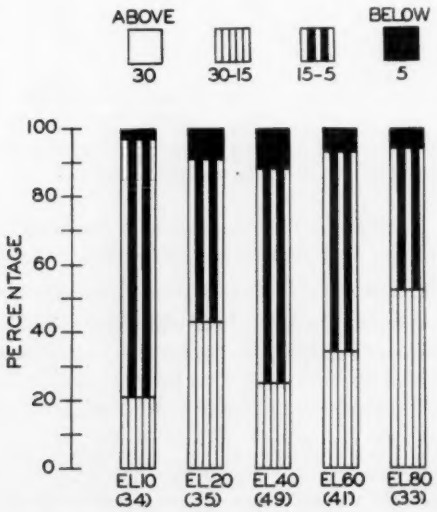

Chart 3.—Effect of diet on the urea ratio of partially nephrectomized rats. The figures in parentheses represent the number of animals.

diet, respectively. When the average value for the animals receiving the EL 10 diet is expressed as 1, the respective ratios for the diets are 1.0, 1.19, 1.36, 1.57 and 1.81. This is interpreted to mean that

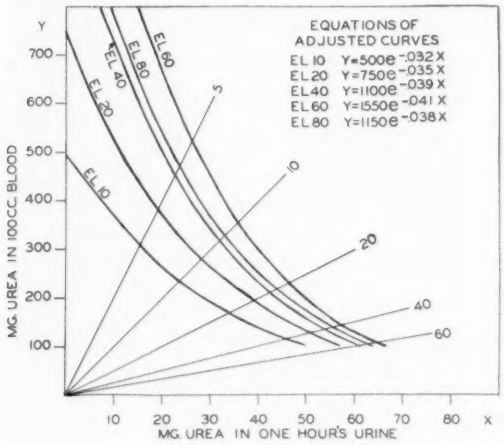

Chart 4.—Relation of the adjusted curves for blood urea and urine urea.

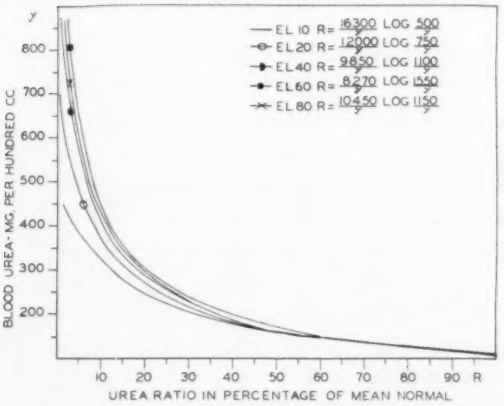
Y
EL 10 R= 16300 LOG 500/Y
EL 20 R= 12000 LOG 750/Y
EL 40 R= 9850 LOG 1100/Y
EL 60 R= 8270 LOG 1550/Y
EL 80 R= 10450 LOG 1150/Y
BLOOD UREA- MG. PER HUNDRED CC.
UREA RATIO IN PERCENTAGE OF MEAN NORMAL
R

Chart 5.—Relation between the concentration of urea in the blood and the urea ratio expressed as percentage of the mean normal value.

hypertrophy of renal tissue progresses with the increase in the ingestion of protein.

Urea Ratios: The incidence of the urea ratios is summarized in chart 3. The group receiving the EL 40 diet had the highest

percentage of ratios below 5. All groups with the exception of that receiving the EL 80 diet had a large percentage of relatively low ratios, indicating marked renal insufficiency.

Effect of Diet on the Blood Urea and Urine Urea: Urea clearance was determined from the ratio $\frac{\text{urea in one hour's urine}}{\text{urea in 100 cc. of blood}}$. At any given urea ratio wide variations in the concentrations of urea in the urine and the blood were obtained for each diet, and these data are presented in chart 4. It is seen that the values for blood urea are progressively increased with increase in the intake of protein at any given urea ratio, except for the animals receiving the EL 80 diet. The inability of animals with severe renal insufficiency to excrete administered urea was accompanied by extraordinarily marked retention of urea in the blood, particularly with the higher concentrations of protein in the diet.

The curves in chart 5 represent an analysis of the effect of diet on the concentration of urea in the blood at any given urea ratio expressed as percentage of the mean normal. The concentration of urea in the blood is not affected appreciably by diet until renal insufficiency is encountered.

SUMMARY

The effect of feeding diets containing various percentages (10, 20, 40, 60 and 80) of dried extracted liver to rats with intact kidneys and to unilaterally nephrectomized and partially nephrectomized rats has been studied.

The ingestion of these diets by intact and by unilaterally nephrectomized animals was accompanied by the following changes:

1. Blood pressure was not affected by diet.

2. The $\frac{\text{heart weight}}{\text{surface area}}$ ratio was fairly constant for all groups except that a low value was observed for the unilaterally nephrectomized rats fed the EL 80 diet.

3. The $\frac{\text{kidney weight}}{\text{surface area}}$ ratio increased progressively with increase in the intake of protein except that the unilaterally nephrectomized rats receiving the EL 80 diet had a low ratio.

4. The urea ratio per gram of kidney was fairly constant for all diets, indicating a direct relation between the degree of renal hypertrophy and the degree of renal function.

The syndrome in partially nephrectomized rats was affected by the percentage of extracted liver in the following manner:

1. The frequency and degree of hypertension were not directly related to the amount of extracted liver in the diet. The most marked hypertension was noted in the animals receiving the EL 20 diet, and

the lowest incidence occurred in the group receiving the EL 80 diet. A close relation between the height of blood pressure and the degree of cardiac hypertrophy was demonstrated for all dietary groups.

2. The total solids of the kidneys increased progressively with increase in ingestion of protein.

3. The animals receiving the EL 40 diet appeared to have the greatest degree of renal insufficiency, as determined by the urea ratio.

4. The concentration of urea in the blood and in the urine at any given ratio increased with increase in the intake of protein except in the group receiving the EL 80 diet.

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

XII. DIETS CONTAINING DRIED EXTRACTED MEAT

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The effect of diets containing varying concentrations of dried whole beef muscle on the intact, the unilaterally nephrectomized and the partially nephrectomized rat has been dealt with in a previous paper.[1] The present report is concerned with the effect of feeding diets containing dried extracted beef muscle on the blood pressure, heart weight, kidney weight and renal function of intact, unilaterally nephrectomized and partially nephrectomized rats.

EXPERIMENTAL METHODS

The experimental procedures have been described in previous papers.[1] Briefly, they are as follows: Partial nephrectomy involved the removal of 80 to 90 per cent of total kidney tissue by a two stage operation; blood pressure readings were obtained by cannulation of the carotid artery; urine was collected for the concentration test for twenty-four hours from the rats deprived of food and water, and a modified urea clearance test of Addis [1] was used for determining renal function.

The five experimental diets used were designated EM 10, EM 20, EM 40, EM 60 and EM 80 in accordance with the percentage of dried extracted meat (table 1), prepared by repeated extraction of cold storage lean beef muscle by hot water (approximately 90 C.). The extracted meat residue was subjected to hydraulic pressure to get rid of the last trace of extract and then dried in steam heated containers. The experimental animals were subjected to the respective dietary regimens for a minimum of seventy-five days and a maximum of one hundred and seventy-five days.

EXPERIMENTAL RESULTS AND ANALYSIS OF OBSERVATIONS

Controls (Intact and Unilaterally Nephrectomized Rats.)—The blood pressure, $\frac{\text{heart weight}}{\text{surface area}}$ and $\frac{\text{kidney weight}}{\text{surface area}}$ ratios, concentration of urine, urea clearance and plasma nonprotein nitrogen concentrations

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1. Chanutin, A., and Ludewig, S.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: V. Diets Containing Whole Dried Meat, Arch. Int. Med. **58**:60 (July) 1936.

for 238 intact and unilaterally nephrectomized rats on the respective diets are summarized in table 2. All of these data could not be obtained for every animal. All rats were in good health when killed.

Blood Pressure and Heart Weight: Of the 147 individual blood pressures for the intact rats, only 4 were above 140 mm. Eleven of the 90 unilaterally nephrectomized animals had blood pressures between 140 and 150 mm. The mean values for blood pressures of the intact and the unilaterally nephrectomized rats on each diet differed so little that the figures for both groups were used in calculating the standard error for the respective diets. It is noted that there is little difference in the mean blood pressures for the various groups. The average $\frac{\text{H. W.}}{\text{S. A.}}$ ratios are fairly constant for all diets. This reflects the constancy of the average blood pressures and the relation between the $\frac{\text{H. W.}}{\text{S. A.}}$ ratio and the blood pressure.

TABLE 1.—*Composition of Rations*

Diet	Concentration of Component in Diet, Percentage						
	Extracted Meat	Starch	Lard	Cod Liver Oil	Dried Yeast	Salt Mixture	Nitrogen
EM 10	10	62	14	5	5	4	1.91
EM 20	20	52	14	5	5	4	3.07
EM 40	40	32	14	5	5	4	5.54
EM 60	60	12	14	5	5	4	8.39
EM 80	80	6	..	4	6	4	11.10

The $\frac{\text{K. W.}}{\text{S. A.}}$ ratios increase progressively with an increase in the intake of protein. If the average $\frac{\text{K. W.}}{\text{S. A.}}$ ratio for the intact animals on the EM 10 diet is considered as 1, the intact animals on the EM 20, the EM 40, the EM 60 and the EM 80 diet show comparative ratios of 1.06, 1.18, 1.26 and 1.50, respectively; if the ratio for the unilaterally nephrectomized animals on the EM 10 diet is considered as 1, the increases are 1.05, 1.25, 1.41 and 1.59, respectively. These results indicate that renal hypertrophy is slightly greater in the unilaterally nephrectomized rats than in the intact animals. It was found that the total solids of the kidneys of the control groups were practically all between 23 and 26 per cent of the wet weight.

The standard errors for the urea ratio $\left(\frac{\text{urea excreted in one hour's urine}}{\text{urea in 100 cc. of blood}}\right)$ are comparatively small, although the individual values vary widely. The average values for the intact animals are 47, 58, 60, 64 and 71 for the groups receiving the EM 10, the EM 20, the EM 40, the EM 60 and the EM 80 diet, respectively; whereas the ratios for the unilaterally

TABLE 2.—*Observations on Control Animals Fed a Variety of Diets*

Renal Condition and Diet	Value	Duration of Experiment, Days	Surface Area	Blood Pressure, Mm.	Heart Weight: Surface Area × 100, Gm.	Kidney Weight: Surface Area × 100, Gm.	Total Solids of Kidneys, Percentage	Twenty-Four Hour Urine Concentration Test: Volume, Cc.	Twenty-Four Hour Urine Concentration Test: Specific Gravity	Urea Ratio	Urea Ratio: Kidney Weight	Nonprotein Nitrogen, Mg. per 100 Cc.
2 kidneys EM 10	Minimum	84	254	116	0.149	0.350	23.3	1.1	1.0230	25	22	22
	Maximum	175	529	144	0.199	0.525	26.3	3.6	1.0769	71	48	51
	Average	105 ± 5.7	334 ± 11.4	130	0.167	0.416 ± 0.009	24.5	1.9	1.0500	47 ± 2.3	36 ± 1.45	33
	Rats	28	28	27	28	28	6	13	13	22	22	15
1 kidney EM 10	Minimum	84	285	118	0.149	0.274	....	1.4	1.0349	29	20	23
	Maximum	175	477	144	0.196	0.378	....	3.3	1.0731	68	49	61
	Average	118 ± 8.3	379 ± 16.2	133	0.174	0.312 ± 0.009	26.0	2.5	1.0541	48 ± 4.1	40 ± 1.26	37
				131 ± 1.3*	0.169 ± 0.002*							
	Rats	12	12	12	12	12	1	8	8	9	9	10
2 kidneys EM 20	Minimum	87	258	112	0.148	0.328	21.2	1.7	1.0363	35	28	29
	Maximum	175	500	136	0.192	0.556	26.8	5.1	1.0628	87	52	53
	Average	106 ± 5.8	343 ± 12.7	125	0.168	0.441 ± 0.013	25.4	3.1	1.0480	58 ± 3.0	37 ± 1.54	39
	Rats	23	23	23	23	23	7	12	11	19	19	13
1 kidney Em 20	Minimum	84	272	104	0.132	0.262	21.0	0.7	1.0315	20	20	26
	Maximum	175	462	146	0.188	0.405	27.3	5.4	1.0784	61	51	45
	Average	116 ± 5.9	356 ± 10.4	127	0.161	0.328 ± 0.009	24.6	2.7	1.0562	42 ± 2.3	36 ± 0.89	34
				126 ± 1.3*	0.165 ± 0.002*							
	Rats	23	23	23	23	23	13	20	19	19	19	8
2 kidneys Em 40	Minimum	87	260	112	0.131	0.386	24.4	0.6	1.0402	39	24	33
	Maximum	173	446	140	0.181	0.609	26.4	4.4	1.0828	84	45	61
	Average	111 ± 4.5	327 ± 10.4	122	0.159	0.491 ± 0.011	25.6	2.0	1.0601	60 ± 2.2	37 ± 1.11	42
	Rats	27	27	27	27	27	11	17	17	25	25	14
1 kidney EM 40	Minimum	87	262	110	0.137	0.284	24.3	1.3	1.0510	28	20	35
	Maximum	175	442	138	0.180	0.520	26.2	4.9	1.0713	71	51	59
	Average	117 ± 8.0	366 ± 12.5	125	0.161	0.393 ± 0.016	25.1	2.9	1.0612	49 ± 2.8	36 ± 0.84	44
				123 ± 1.3*	0.160 ± 0.002*							
	Rats	17	17	17	17	17	5	11	11	17	17	12
2 kidneys EM 60	Minimum	75	265	114	0.133	0.435	24.2	1.4	1.0442	41	27	35
	Maximum	175	511	142	0.185	0.630	26.4	4.5	1.0795	89	50	70
	Average	113 ± 6.5	332 ± 11.3	128	0.156	0.525 ± 0.012	25.1	2.6	1.0598	64 ± 3.0	38 ± 1.21	45
	Rats	26	26	26	26	25	10	16	16	22	22	14
1 kidney EM 60	Minimum	89	295	120	0.145	0.364	23.7	1.6	1.0300	42	26	48
	Maximum	182	437	158	0.188	0.575	24.2	5.5	1.0625	59	43	71
	Average	117 ± 6.7	364 ± 10.0	133	0.163	0.441 ± 0.010	23.9	3.2	1.0546	49 ± 1.5	33 ± 0.90	54
				130 ± 1.5*	0.159 ± 0.002*							
	Rats	16	16	16	16	16	4	10	10	12	12	8
2 kidneys EM 80	Minimum	89	276	114	0.149	0.460	22.4	0.7	1.0258	51	22	32
	Maximum	185	407	154	0.212	0.775	25.6	4.7	1.0691	93	45	62
	Average	123 ± 4.8	348 ± 5.7	127	0.170	0.625 ± 0.016	24.0	2.8	1.0501	71 ± 2.0	32 ± 1.00	42
	Rats	44	44	44	44	44	22	22	22	30	30	11
1 kidney EM 80	Minimum	88	240	110	0.125	0.340	22.0	3.1	1.0405	36	21	38
	Maximum	185	437	150	0.183	0.694	24.6	4.8	1.0585	62	43	74
	Average	116 ± 7.1	333 ± 9.6	126	0.158	0.496 ± 0.022	23.2	3.8	1.0464	49 ± 2.3	29 ± 0.99	59
				127 ± 1.2*	0.166 ± 0.002*							
	Rats	22	22	21	21	22	13	5	5	13	12	8

* Average and standard error for control animals on a specific diet.

nephrectomized animals on the same diets are 48, 42, 49, 49 and 49. The ratios for the unilaterally nephrectomized rats appear to be remarkably constant regardless of diet, indicating perhaps less flexibility of renal function.

Increases of the kidney weights and urea ratios for the intact rats are strikingly proportional, as shown by the constancy of the $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratios of 36, 37, 37, 38 and 32 for the rats on the EM 10, the EM 20, the EM 40, the EM 60 and the EM 80 diet, respectively; whereas the varied ratios for the unilaterally nephrectomized rats on these diets are 40, 36, 36, 33 and 29, respectively. The ratios for the intact rats are constant, but there is a decrease in the values for the unilaterally nephrectomized rats.

In general, there appears to be little difference in the urinary volumes or specific gravities of the urines obtained during a concentration test for the intact and the unilaterally nephrectomized rats on the various diets. The majority of the urinary volumes were between 1 and 3 cc., and most of the specific gravities were between 1.0500 and 1.0600.

The nonprotein nitrogen concentration of the blood plasma of all intact rats remained fairly constant. There was little difference in these values for the intact and the unilaterally nephrectomized animals on the first three diets. The unilaterally nephrectomized rats on the EM 60 and the EM 80 diet showed values distinctly higher than those for the corresponding intact animals.

On the basis of the foregoing results, the following values have been taken as the limits of normal: blood pressures below 140 mm. of mercury, urinary volumes below 5 cc., urinary specific gravities above 1.0400, urinary protein content below 0.05 Gm. and urea ratios above 30.

Partially Nephrectomized Rats.—The data for partially nephrectomized rats in good health on diets EM 10, EM 20, EM 40, EM 60 and EM 80 are shown in tables 3 to 7. Charts 1 to 8 were prepared to facilitate comparisons of the effects of the various diets on the blood pressure, the total solids of the kidneys, in relation to surface area, the urinary volume, the specific gravity and urinary protein as determined by the concentration test and the urea ratio and its relation to the urea in the blood and the urine.

Blood Pressure: The effects of the diets on blood pressure are summarized in chart 1. The percentage of animals with blood pressures above the upper limits of normal (140 mm.) was greatest in the groups receiving the EM 40 and the EM 60 diet. However, the percentage of animals with pressures above 180 mm. was about the same in the groups fed the first four diets and appreciably less in the group fed the EM 80 diet. It is of interest that on further analysis (not in the chart) the percentage incidence of blood pressures above 200 mm. was

TABLE 3.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 10 per Cent Dried Extracted Beef Muscle*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Kidney Weight / Surface Area × 100	Kidney Total Solids, %	Twenty-Four Hour Urine Concentration Test: Volume, Cc.	Specific Gravity	Albumin, Gm.	Urea Ratio	Non-protein Nitrogen, Mg. per 100 Cc.
1	75	307	154	0.181	0.194	....	5.0	1.0297	0.041	11	72
2	75	306	156	0.175	0.237	....	3.8	1.0259	.....	15	64
3	75	289	150	0.173	0.209	....	4.5	1.0277	0.007	13	75
4	75	242	212	0.208	0.126	....	7.3	1.0203	0.056	8	87
5	77	260	128	0.193	0.276	....	6.0	1.0325	0.017	19	49
6	77	266	126	0.184	0.202	....	3.8	1.0359	.....	20	61
7	77	258	138	0.174	0.230	....	3.7	1.0391	.....	20	42
8	77	275	156	0.234	0.237	....	12.7	1.0222	0.085	19	53
9	77	356	136	0.188	0.232	....	5.7	1.0381	0.007	34	50
10	84	339	182	0.196	0.154	....	10.7	1.0177	0.067	15	72
11	84	242	218	0.244	0.258	....	5.5	1.0315	0.107	17	..
12	85	350	...	0.186	0.228	....	3.5	1.0433	.....	22	54
13	85	322	...	.....	0.208	....	4.0	1.0398	0.005	25	..
14	85	330	176	0.206	0.245	....	6.8	1.0333	0.048	18	43
15	85	356	160	0.181	0.245	....	8.2	1.0346	0.096	24	40
16	85	302	160	0.200	0.239	....	7.3	1.0285	0.038	23	32
17	85	348	196	0.257	0.289	....	9.0	1.0350	0.197	16	50
18	85	289	160	0.205	0.235	....	5.6	1.0315	0.055	17	46
19	89	238	210	0.229	0.220	....	6.0	1.0217	0.040	..	76
20	89	323	152	0.186	0.224	....	4.0	1.0315	.....	18	57
21	89	262	206	0.192	0.246	....	2.9	1.0535	.....	10	72
22	89	320	104	0.169	0.208	....	4.0	1.0319	.....	16	63
23	102	297	192	0.211	0.223	....	8.8	1.0189	0.041	..	64
24	107	248	130	0.140	0.227	23.8	4.8	1.0240	0.003	17	..
25	107	230	124	0.148	0.191	21.6	3.1	1.0270	0.001	11	..
26	107	260	156	0.189	0.259	19.3	5.9	1.0271	0.038	13	..
27	107	220	136	0.168	0.237	20.6	3.1	1.0322	.....	9	..
28	107	308	172	0.174	0.283	20.2	3.3	1.0294	.....	11	67
29	107	304	136	0.171	0.198	23.0	3.4	1.0328	.....	20	40
30	107	244	152	0.197	0.234	20.0	4.1	1.0273	.....	8	68
31	107	258	134	0.152	0.276	22.0	1.7	1.0484	.....	18	55
32	107	230	156	0.162	0.223	21.8	2.0	1.0383	.....	13	46
33	107	232	...	.....	0.244	24.2	3.8	1.0314	.....	15	..
34	109	355	128	0.179	0.221	....	4.4	1.0327	0.033	..	61
35	109	280	138	0.164	0.223	....	2.9	1.0359	.....	16	61
36	110	280	184	0.228	0.272	19.8	6.7	1.0235	0.063	12	..
37	110	230	160	0.173	0.218	19.8	5.4	1.0227	0.007	8	..
38	110	222	160	0.229	0.158	16.8	8.7	1.0135	0.010	3	..
39	110	196	250	0.229	0.139	18.0	6.3	1.0173	0.017	..	..
40	114	276	164	0.214	0.338	19.4	4.5	1.0298	0.044	14	75
41	114	254	230	0.247	0.310	16.5	7.0	1.0202	.....	5	84
42	114	341	146	0.206	0.239	19.7	4.8	1.0311	0.048	11	83
43	114	308	164	0.192	0.227	22.4	8.7	1.0207	0.037	10	80
44	114	313	214	0.256	0.256	19.8	5.7	1.0311	0.097	7	..
45	114	326	174	0.222	0.204	20.2	7.6	1.0358	0.209	7	75
46	114	285	192	0.250	0.338	17.3	6.7	1.0311	0.167	10	96
47	114	302	166	0.197	0.270	17.0	7.0	1.0258	0.029	11	76
48	114	301	132	0.202	0.320	22.0	3.7	1.0386	.....	15	69
49	116	216	216	0.219	0.165	15.7	4.5	1.0149	0.025	3	..
50	116	299	144	0.159	0.208	23.0	5.7	1.0172	0.024	9	..
51	116	274	202	0.192	0.206	19.0	7.8	1.0227	0.088	6	..
52	116	250	160	0.200	0.170	18.3	5.8	1.0167	0.007	4	..
53	116	283	184	0.222	0.213	18.4	5.2	1.0235	0.010	5	..
54	116	276	140	0.178	0.165	22.4	5.3	1.0257	0.008	11	..
55	116	230	164	0.212	0.251	19.2	8.1	1.0220	0.034	12	..
56	116	270	160	0.165	0.236	20.8	2.6	1.0340	.....	15	..
57	116	254	134	0.179	0.222	23.9	2.5	1.0481	.....	21	..
58	116	252	170	0.249	0.172	18.4	9.9	1.0201	0.085	8	..
59	133	354	156	0.183	0.196	....	8.8	1.0194	0.041	..	63
60	133	270	162	0.182	0.228	....	4.7	1.0333	0.110	..	61
61	136	334	142	0.188	0.172	....	14.5	1.0184	0.070	..	56
62	136	285	128	0.166	0.253	....	2.9	1.0370	.....	..	46
63	158	376	186	0.212	0.271	....	12.5	1.0218	.....	12	61

TABLE 4.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 20 per Cent Dried Extracted Beef Muscle*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Kidney Weight / Surface Area × 100	Kidney Total Solids, %	Twenty-Four Hour Urine Concentration Test: Volume, Cc.	Specific Gravity	Albumin, Gm.	Urea Ratio	Non-protein Nitrogen, Mg. per 100 Cc.
1	75	286	116	0.164	0.264	....	5.3	1.0297	0.041	..	59
2	90	242	122	0.167	0.289	....	4.0	1.0313	.....	..	..
3	90	379	158	0.172	0.256	....	9.3	1.0262	0.086	..	55
4	90	306	138	0.167	0.268	....	5.3	1.0313	0.101	..	79
5	90	295	152	0.170	0.236	....	3.5	1.0358	.....	..	51
6	90	306	128	0.162	0.278	....	5.0	1.0309	0.041	..	67
7	103	376	158	0.186	0.396	....	....	.....	.....	..	118
8	103	313	138	0.200	0.363	....	17.1	1.0176	0.280	..	82
9	103	314	124	0.161	0.246	....	8.5	1.0232	0.065	..	72
10	103	419	226	0.229	0.455	....	15.7	1.0204	0.297	..	123
11	104	427	194	0.206	0.436	....	11.5	1.0210	0.155	..	129
12	107	283	152	0.174	0.215	21.4	5.0	1.0343	.....	5	111
13	107	307	124	0.152	0.237	23.4	7.5	1.0311	0.005	19	..
14	107	314	154	0.199	0.296	18.3	14.5	1.0168	0.032	6	101
15	107	240	196	0.190	0.355	15.5	9.0	1.0179	0.090	4	..
16	107	318	182	0.216	0.333	15.1	10.0	1.0196	0.013	5	108
17	107	230	156	0.144	0.240	21.6	1.1	1.0456	.....	12	69
18	107	376	156	0.171	0.278	20.1	7.3	1.0268	0.035	..	87
19	107	308	174	0.183	0.259	19.3	6.8	1.0269	0.039	9	87
20	107	364	132	0.190	0.241	22.0	7.8	1.0251	0.035	9	82
21	107	356	156	0.175	0.241	23.2	3.9	1.0366	.....	23	58
22	107	268	138	0.135	0.208	20.4	4.0	1.0344	0.009	12	74
23	107	265	150	0.164	0.295	18.2	6.7	1.0261	0.071	12	90
24	107	304	134	0.175	0.275	19.8	8.9	1.0224	0.065	6	83
25	107	250	124	0.137	0.275	18.0	4.5	1.0257	0.008	14	69
26	107	242	130	0.172	0.318	19.2	6.0	1.0324	0.100	16	125
27	107	234	198	0.234	0.192	16.4	8.6	1.0148	0.034	3	117
28	107	250	138	0.190	0.382	18.3	....	.....	.....	15	105
29	107	248	208	0.294	0.413	14.1	....	.....	.....	5	125
30	119	323	150	0.189	0.252	20.1	12.3	1.0206	0.036	10	..
31	119	355	166	0.250	0.370	13.9	22.8	1.0138	0.078	6	..
32	119	299	188	0.230	0.313	16.2	12.2	1.0230	0.145	12	..
33	119	318	212	0.222	0.188	16.2	19.4	1.0124	0.051	6	..
34	119	275	176	0.217	0.358	15.8	15.0	1.0175	0.163	8	..
35	120	265	220	0.265	0.757	16.5	13.2	1.0167	0.153	5	..
36	120	299	148	0.192	0.307	18.8	7.9	1.0258	0.103	11	..
37	120	323	136	0.166	0.242	22.9	5.9	1.0308	.....	17	..
38	120	345	180	0.194	0.317	18.7	11.4	1.0248	0.146	10	..
39	120	330	134	0.179	0.295	23.0	6.6	1.0270	0.040	12	..
40	120	306	116	0.188	0.301	20.5	6.0	1.0326	0.064	21	..
41	120	265	132	0.150	0.201	21.9	4.6	1.0180	0.002	16	..
42	120	283	138	0.165	0.222	22.9	7.1	1.0248	0.024	16	..
43	120	274	160	0.158	0.244	20.0	5.8	1.0188	0.052	12	..
44	134	411	164	0.222	0.602	....	17.1	1.0192	0.204	..	80
45	134	421	138	0.169	0.249	....	5.2	1.0373	0.079	..	54
46	134	425	130	0.180	0.216	....	8.2	1.0291	0.042	..	..
47	134	362	158	0.164	0.267	....	8.5	1.0207	0.089	..	..
48	134	370	156	0.183	0.310	....	17.1	1.0146	0.120	..	83
49	134	386	184	0.208	0.196	....	16.5	1.0139	0.046	..	97
50	134	265	196	0.226	0.332	....	7.7	1.0207	0.158	..	97
51	134	402	204	0.196	0.565	....	9.5	1.0260	0.250	..	64
52	134	366	174	0.202	0.269	....	15.3	1.0153	0.141	..	100
53	164	334	168	0.162	0.266	....	6.7	1.0274	.....	11	110
54	164	310	190	0.186	0.298	....	12.0	1.0255	.....	8	108
55	164	275	144	0.255	0.323	....	11.8	1.0180	.....	3	133
56	164	389	230	0.246	0.391	....	5.5	1.0144	.....	6	129
57	175	452	128	0.179	0.276	....	10.7	1.0299	.....	..	58
58	175	439	188	0.214	0.476	....	24.0	1.0166	0.312	6	..
59	175	324	166	0.190	0.450	....	12.2	1.0228	0.208	12	74

as follows: EM 10, 15; EM 20, 10; EM 40, 6; EM 60, 0; and EM 80, 1. The highest blood pressure in this series (250 mm.) was obtained in a rat on the EM 10 diet.

TABLE 5.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 40 per Cent Dried Extracted Beef Muscle*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Kidney Weight / Surface Area × 100	Kidney Total Solids, %	Twenty-Four Hour Urine Concentration Test: Volume, Cc.	Specific Gravity	Albumin, Gm.	Urea Ratio	Nonprotein Nitrogen, Mg. per 100 Cc.
1	75	306	154	0.186	0.311	....	9.5	1.0248	0.062	13	91
2	75	334	146	0.198	0.240	....	21.4	1.0173	0.192	9	131
3	75	295	142	0.187	0.376	....	7.1	1.0330	0.084	15	85
4	75	270	170	0.196	0.205	....	11.7	1.0181	0.053	7	155
5	75	306	174	0.194	0.368	....	11.1	1.0236	0.098	12	111
6	111	306	144	0.162	0.362	....	4.9	1.0380	0.080	17	..
7	113	320	136	0.172	0.437	16.8	13.6	1.0167	.....	..	150
8	113	250	164	0.188	0.280	18.8	9.8	1.0190	0.094	5	..
9	113	328	138	0.171	0.420	16.7	15.6	1.0180	0.111	..	129
10	113	278	...	.....	0.437	14.4	13.7	1.0125	0.056	..	..
11	113	302	182	0.187	0.380	14.4	17.0	1.0129	0.070	5	200
12	113	306	178	0.165	0.480	17.2	5.4	1.0249	0.048	14	121
13	113	248	128	0.153	0.265	17.2	5.7	1.0235	0.018	13	111
14	113	295	156	0.171	0.422	16.5	6.7	1.0249	0.046	..	114
15	113	372	162	0.199	0.375	17.9	18.5	1.0197	0.220	14	166
16	113	252	134	0.153	0.366	18.5	7.5	1.0249	0.061	15	..
17	113	254	162	0.187	0.272	19.1	7.2	1.0203	0.036	9	..
18	113	336	158	0.194	0.324	17.5	11.0	1.0166	0.023	12	132
19	118	268	...	.....	0.314	18.4	10.7	1.0192	0.017	11	..
20	118	310	138	0.176	0.360	18.4	13.9	1.0195	0.070	3	..
21	118	254	144	0.163	0.370	18.7	8.6	1.0241	0.053	4	..
22	118	246	166	0.172	0.412	18.9	6.5	1.0272	0.056	11	..
23	118	260	184	0.186	0.370	19.8	8.1	1.0220	0.050	9	..
24	118	341	158	0.195	0.386	19.2	11.1	1.0239	0.095	11	..
25	118	276	192	0.184	0.444	14.1	12.1	1.0173	0.050	4	..
26	118	318	210	0.212	0.428	14.7	15.5	1.0143	0.073	4	..
27	120	320	144	0.164	0.336	17.1	14.0	1.0195	0.069	..	..
28	120	238	176	0.170	0.538	12.6	13.6	1.0139	0.075	..	..
29	120	341	186	0.186	0.548	13.0	19.8	1.0162	0.131	8	..
30	120	314	162	0.167	0.322	18.0	17.1	1.0165	0.060	4	..
31	120	250	138	0.196	0.326	18.3	11.2	1.0215	0.087	10	..
32	120	283	156	0.216	0.371	15.2	17.3	1.0161	0.208	..	..
33	127	364	168	0.183	0.415	....	18.3	1.0159	0.147	..	151
34	127	364	182	0.215	0.361	....	21.0	1.0137	0.126	..	184
35	127	307	148	0.174	0.370	....	10.0	1.0212	0.134	..	113
36	127	313	126	0.170	0.480	....	10.4	1.0228	0.210	..	150
37	127	373	190	0.240	.....	....	20.8	1.0144	0.227	..	272
38	127	343	176	0.236	0.260	....	21.0	1.0129	0.080	..	272
39	139	310	172	0.196	0.558	....	17.7	1.0197	.....	11	172
40	139	386	186	0.200	0.728	....	22.7	1.0180	.....	9	200
41	146	334	162	0.156	0.326	....	13.4	1.0178	0.108	13	..
42	146	268	166	0.202	0.382	....	10.8	1.0189	0.202	2	370
43	146	323	216	0.196	0.460	....	17.6	1.0215	0.338	11	180
44	146	341	166	0.214	0.436	....	16.2	1.0210	.....	10	148
45	148	326	146	0.190	0.410	....	15.2	1.0202	0.221	12	196
46	148	370	152	0.189	0.340	....	19.5	1.0202	0.258	13	125
47	148	291	182	0.171	0.640	....	16.9	1.0148	0.120	5	..
48	148	280	176	0.190	0.440	....	11.3	1.0183	0.212	11	155
49	148	254	224	0.236	0.228	....	15.6	1.0166	0.152	2	387
50	173	348	144	0.193	0.289	....	18.6	1.0180	.....	15	133
51	173	313	126	0.145	0.296	....	....	.....	.....	..	53

The correlation coefficients and probable errors were calculated for blood pressure and $\frac{\text{H. W.}}{\text{S. A.}}$ ratios for each diet as follows: EM 10, 0.67 ± 0.05; EM 20, 0.52 ± 0.06; EM 40, 0.60 ± 0.06; EM 60, 0.14 ± 0.10, and EM 80, 0.33 ± 0.07. These results for the partially neph-

rectomized animals show a substantial relation for the first three diets and a negligible relation for the EM 60 diet and a slight relation for the EM 80 diet.

TABLE 6.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 60 per Cent Dried Extracted Beef Muscle*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Kidney Weight / Surface Area × 100	Kidney Total Solids, %	Twenty-Four Hour Urine Concentration Test: Volume, Cc.	Specific Gravity	Albumin, Gm.	Urea Ratio	Nonprotein Nitrogen, Mg. per 100 Cc.
1	75	348	144	0.210	0.520	....	10.8	1.0268	0.082	25	133
2	75	333	144	0.212	0.413	....	17.8	1.0155	0.107	12	231
3	75	232	166	0.168	0.354	....	9.5	1.0156	0.062	8	250
4	75	306	142	0.160	0.401	....	8.5	1.0238	0.050	11	143
5	103	220	...	.....	0.317	17.1	8.1	1.0206	.....	6	..
6	103	278	146	0.161	0.402	18.3	6.5	1.0273	0.040	20	..
7	103	252	192	0.162	0.495	14.5	7.4	1.0223	0.069	12	..
8	103	256	196	0.157	0.558	13.4	11.3	1.0207	0.190	8	..
9	103	295	172	0.166	0.467	13.4	16.8	1.0170	0.096	13	..
10	103	258	172	0.161	0.437	15.7	10.6	1.0162	0.042	14	..
11	103	299	180	0.185	0.550	16.8	10.3	1.0219	.....	15	..
12	103	304	176	0.188	0.652	13.7	12.5	1.0176	0.148	6	..
13	103	272	174	0.152	0.468	16.3	8.0	1.0241	0.089	8	..
14	104	379	126	0.190	0.394	....	7.8	1.0323	0.095	29	126
15	104	299	134	0.184	0.396	....	9.0	1.0256	0.180	13	177
16	104	334	126	0.165	0.260	....	15.0	1.0191	0.044	16	149
17	104	280	124	0.169	0.330	....	3.7	1.0421	.....	28	..
18	104	280	124	0.180	0.362	....	8.4	1.0261	0.070	16	149
19	104	341	138	0.173	0.382	....	11.4	1.0237	0.102	17	177
20	105	240	190	0.177	0.550	....	8.2	1.0177	0.000	28	150
21	105	242	182	0.212	0.545	....	9.5	1.0186	0.222	22	333
22	108	292	136	0.174	0.226	....	11.3	1.0244	0.320	..	..
23	113	244	154	0.189	0.376	....	11.4	1.0188	0.123	7	192
24	113	238	156	0.155	0.340	....	6.3	1.0300	0.058	10	142
25	113	302	124	0.145	0.338	....	12.5	1.0236	0.102	17	152
26	113	203	196	0.238	0.412	....	10.8	1.0156	0.122	2	393
27	113	244	142	0.195	0.347	....	10.2	1.0209	0.145	7	204
28	113	220	176	0.168	0.525	....	11.3	1.0158	0.092	3	288
29	113	310	154	0.164	0.384	....	12.6	1.0163	0.103	13	152
30	118	280	176	0.168	0.496	....	9.2	1.0207	0.048	11	110
31	118	276	184	0.176	0.366	....	12.5	1.0195	0.104	8	133
32	118	274	142	0.167	0.392	....	14.7	1.0168	0.057	5	210
33	118	314	146	0.187	0.487	....	15.8	1.0215	0.174	..	160
34	118	268	166	0.164	0.505	....	5.6	1.0378	0.071	22	170
35	118	299	142	0.174	0.370	....	8.9	1.0270	0.062	11	144
36	118	302	142	0.174	0.456	....	15.3	1.0191	.....	10	210
37	118	254	176	0.173	0.400	18.7	10.2	1.0189	0.090	10	..
38	118	278	160	0.173	0.480	18.4	11.9	1.0188	0.116	11	152
39	120	358	158	0.181	0.421	....	17.3	1.0203	0.166	..	150
40	134	334	154	0.209	0.428	....	20.0	1.0179	0.168	..	326
41	136	328	180	0.230	0.707	....	18.0	1.0137	0.061	..	100
42	136	345	182	0.229	0.417	....	17.7	1.0158	0.147	..	90
43	136	348	158	0.189	.....	....	6.7	1.0230	0.008	..	80
44	151	268	152	0.177	0.322	....	12.1	1.0151	0.151	7	570
45	151	248	150	0.135	0.252	....	10.8	1.0142	0.032	..	200
46	151	256	182	0.165	0.333	....	6.8	1.0183	0.050	6	..
47	175	278	186	0.186	0.781	....	14.0	1.0149	0.130	3	334
48	175	310	184	0.199	0.503	....	15.2	1.0162	0.117	2	340

Kidneys: The data for total solids of the kidney remnants expressed in milligrams per hundred square centimeters of surface area are presented in chart 2, and the average values are as follows: 47 ± 1.8; 52 ± 1.3; 65 ± 1.7; 70 ± 2.4, and 79 ± 1.6 for the groups fed the EM 10, the EM 20, the EM 40, the EM 60 and the EM 80 diet.

TABLE 7.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 80 per Cent Dried Extracted Beef Muscle*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight: Surface Area × 100	Kidney Weight: Surface Area × 100	Kidney Total Solids, %	Twenty-Four Hour Urine Concentration Test: Volume, Cc.	Specific Gravity	Albumin, Gm.	Urea Ratio	Non-protein Nitrogen, Mg. per 100 Cc.
1	88	304	116	0.161	0.430	....	....	.....	.....	..	56
2	100	286	148	0.165	0.675	15.2	8.8	1.0216	.....	16	..
3	100	288	124	0.143	0.500	16.3	5.8	1.0251	0.008	19	170
4	100	207	152	0.157	0.374	18.5	8.0	1.0182	0.037	10	..
5	100	260	136	0.154	0.592	15.2	9.0	1.0187	0.005	11	190
6	100	207	188	0.160	0.543	15.8	5.4	1.0208	0.041	6	..
7	100	275	146	0.159	0.570	15.5	14.1	1.0163	0.109	12	240
8	102	228	202	0.215	0.835	....	....	.....	.....	6	..
9	102	265	160	0.162	0.526	....	....	.....	.....	18	..
10	102	248	138	0.153	0.515	....	....	.....	.....	15	..
11	102	266	190	0.190	0.546	....	....	.....	.....	18	..
12	102	276	148	0.161	0.484	....	....	.....	.....	25	..
13	102	212	166	0.156	0.470	....	....	.....	.....	18	..
14	107	232	190	0.190	0.585	12.5	12.1	1.0141	0.064	5	400
15	107	234	148	0.151	0.603	17.0	16.6	1.0182	0.156	..	..
16	107	205	156	0.158	0.530	18.4	17.5	1.0162	0.128	..	..
17	107	270	138	0.149	0.400	18.2	13.6	1.0225	0.216	13	128
18	107	207	134	0.145	0.380	18.8	7.5	1.0158	0.017	..	..
19	107	217	132	0.137	0.346	19.7	6.0	1.0228	0.032	14	..
20	107	228	152	0.147	0.435	16.9	6.7	1.0238	0.106	10	..
21	108	301	148	0.181	0.562	15.6	13.1	1.0172	0.121	9	200
22	108	234	158	0.174	0.515	16.5	7.4	1.0181	0.054	12	..
23	108	254	150	0.140	0.502	15.6	8.7	1.0175	0.120	9	..
24	108	274	144	0.169	0.546	15.7	12.3	1.0156	.....	13	143
25	108	297	148	0.169	0.608	13.1	14.0	1.0167	0.106	..	300
26	108	252	162	0.149	0.577	15.4	7.2	1.0225	0.112	20	212
27	108	230	158	0.173	0.377	18.8	7.2	1.0228	0.096	18	..
28	108	228	134	0.169	0.462	20.0	4.7	1.0291	0.048	17	..
29	108	203	186	0.201	0.508	13.5	10.1	1.0112	0.020	5	..
30	108	246	158	0.185	0.510	14.8	11.0	1.0178	0.134	9	..
31	108	258	158	0.208	0.656	13.1	14.9	1.0152	0.107	6	400
32	108	266	168	0.149	0.487	16.7	9.1	1.0216	.....	19	200
33	108	228	142	0.153	0.390	17.4	7.5	1.0217	0.051	15	..
34	108	250	138	0.155	0.460	19.6	8.5	1.0276	0.113	..	91
35	109	250	136	0.172	0.450	....	6.3	1.0305	0.060	14	136
36	109	265	126	0.157	0.379	....	6.8	1.0297	0.008	15	111
37	109	274	136	0.174	0.440	....	11.5	1.0199	0.052	13	125
38	109	256	160	0.184	0.577	....	10.7	1.0180	0.153	7	232
39	109	301	124	0.147	0.434	....	5.9	1.0356	0.021	19	111
40	109	302	142	0.182	0.601	....	13.2	1.0196	0.100	..	154
41	109	231	192	0.228	0.686	....	....	.....	.....	7	..
42	109	320	192	0.204	0.765	....	....	.....	.....	..	..
43	109	250	138	0.156	0.470	....	....	.....	.....	14	..
44	109	242	178	0.172	0.586	....	....	.....	.....	14	..
45	109	216	152	0.192	0.474	....	....	.....	.....	8	..
46	109	252	164	0.181	0.470	....	....	.....	.....	13	..
47	109	328	134	0.159	0.497	....	....	.....	.....	33	..
48	110	291	138	0.216	0.412	....	17.6	1.0156	0.091	..	148
49	110	262	158	0.183	0.466	....	14.1	1.0152	0.092	7	167
50	110	230	138	0.168	0.417	....	4.3	1.0337	0.062	10	..
51	110	242	126	0.158	0.322	....	4.9	1.0317	0.029	..	..
52	110	265	146	0.156	0.398	....	7.7	1.0231	0.007	12	133
53	110	302	132	0.174	0.837	....	18.9	1.0180	0.185	17	136
54	111	234	162	0.185	0.336	16.3	11.5	1.0150	0.089	10	..
55	111	301	142	0.200	0.547	14.3	13.3	1.0191	0.080	19	200
56	111	295	156	0.211	0.605	14.7	16.6	1.0182	0.156	17	216
57	111	283	156	0.203	0.580	15.2	17.5	1.0162	0.128	..	288
58	111	205	146	0.146	0.460	16.9	8.9	1.0203	0.144	11	..
59	111	250	138	0.177	0.508	15.1	....	.....	.....	10	270
60	111	231	168	0.163	0.465	15.9	....	.....	.....	11	..
61	111	231	168	0.183	0.623	14.6	....	.....	.....	12	..
62	111	226	158	0.155	0.502	14.9	....	.....	.....	8	..
63	119	286	122	0.179	0.340	....	....	.....	.....	..	..
64	123	272	166	0.202	0.749	....	8.3	1.0207	.....	..	..
65	127	314	158	0.229	0.505	....	11.0	1.0210	0.125	..	154
66	132	238	124	0.215	0.384	....	....	.....	.....	..	..
67	133	302	170	0.220	0.732	....	13.2	1.0177	0.152	..	258
68	140	292	172	0.210	0.738	....	9.2	1.0217	0.127	..	285
69	140	292	144	0.180	0.543	....	4.8	1.0353	0.028	..	125
70	140	234	150	0.197	0.820	....	10.1	1.0176	0.117	..	278
71	140	274	158	0.182	0.640	....	8.5	1.0193	.....	..	192
72	142	292	142	0.203	0.737	....	14.1	1.0207	0.272	..	160
73	147	289	146	0.245	.....	....	20.3	1.0139	0.183	..	400
74	147	272	182	0.212	0.793	....	12.0	1.0166	0.121	..	266
75	154	362	136	0.234	0.498	....	....	.....	.....	..	..
76	154	268	170	0.183	0.497	....	....	.....	.....	..	..
77	155	340	160	0.222	0.563	....	12.4	1.0219	0.150	..	100
78	155	283	165	0.191	0.490	....	6.8	1.0311	0.104	..	110
79	155	341	190	0.338	0.865	....	25.8	1.0153	0.289	..	307
80	171	314	196	0.214	0.518	....	8.0	1.0202	0.159	..	183
81	171	318	174	0.240	0.573	....	9.1	1.0207	0.091	..	308

respectively. If the average value for the group fed the EM 10 diet is considered as 1, the ratios for those fed the respective diets are 1.0, 1.11, 1.38, 1.49 and 1.68, representing a proportional increase. These ratios are quite comparable to figures obtained for the unilaterally nephrectomized rats and to a lesser extent for the intact rats.

Nonprotein Nitrogen: Retention of nitrogen in the blood seems to vary with the intake of protein. The average values in milligrams of nonprotein nitrogen of plasma for each diet are as follows: EM 10, 61; EM 20, 90; EM 40, 165; EM 60, 202, and EM 80, 199. These values are all much higher than those obtained for the control groups

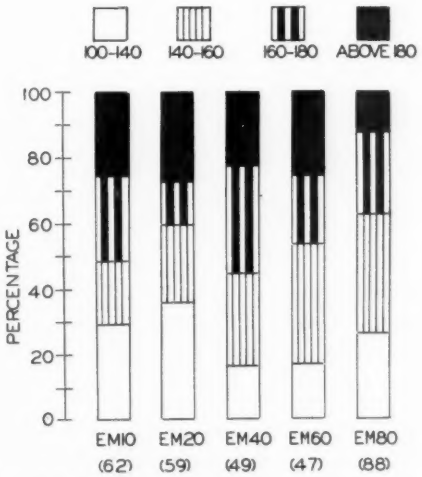

Chart 1.—Effect of diet on the blood pressure of partially nephrectomized rats. In this chart and in similar charts the figures in parentheses represent the number of animals.

on similar diets. There were marked individual variations, as shown in the tables for the respective diets.

RENAL FUNCTION

Urine Concentration Test.—The effect of various diets on the urinary volume is shown in chart 3. It is seen that there is a marked progressive increase in the incidence and degree of polyuria with the first three diets. Forty-two per cent of the animals on the EM 40 diet excreted over 15 cc. of urine, which represents the greatest degree of polyuria in these experiments. In view of the small amount of urine excreted by the control rats, these results indicate a marked

disturbance in the factors concerned in the retention or reabsorption of water in the kidney.

Chart 4 shows the effect of diet on the specific gravity of the urine after correction for the effect of proteinuria. It is noted that there is a progressive increase in the percentage of animals having low specific gravities in groups fed the EM 10, the EM 20 and the EM 40 diet. The marked preponderance of specific gravities between 1.0100 and 1.0200 tends to reflect the large amounts of water lost by these animals.

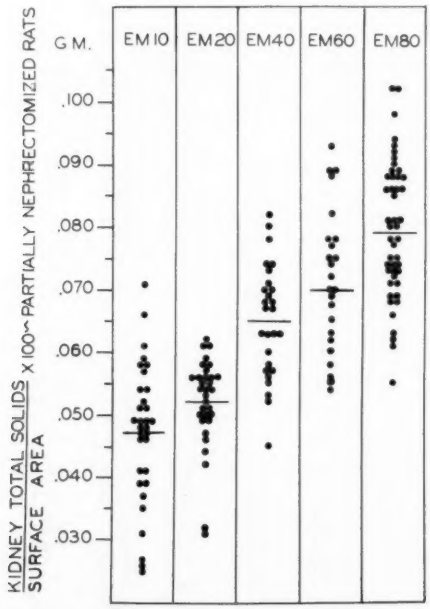

Chart 2.—Effect of diet on the total solids of the kidneys per hundred square centimeters of surface area of partially nephrectomized rats.

Chart 5 summarizes the effect of diet on the excretion of protein. The greatest output of protein was noted in the group fed the EM 40 diet. The percentage incidence of animals excreting more than 0.2 Gm. of protein daily was about the same for the groups fed the EM 10, the EM 60 and the EM 80 diet. The amount of dietary protein does not appear to be related to the degree of proteinuria.

It is interesting to note that the maximal change in urinary volume, specific gravity and proteinuria was attained with the EM 40 diet. There seems to be no relation between the retention of nitrogen or the

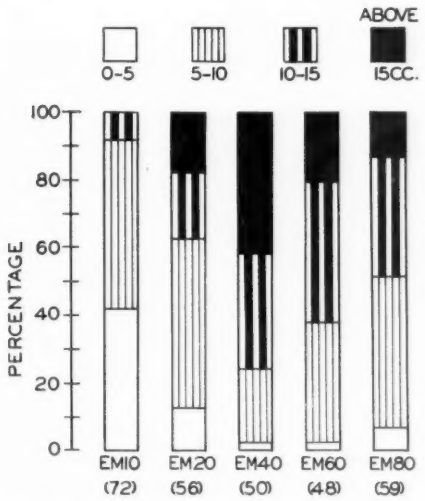

Chart 3.—Effect of diet on the urinary volume of partially nephrectomized rats.

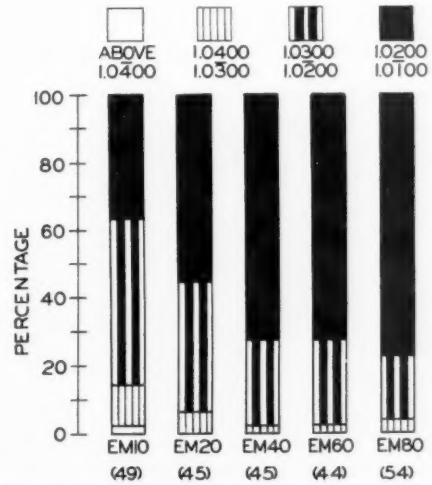

Chart 4.—Effect of diet on the specific gravity (after correction for protein) of the urine of partially nephrectomized rats.

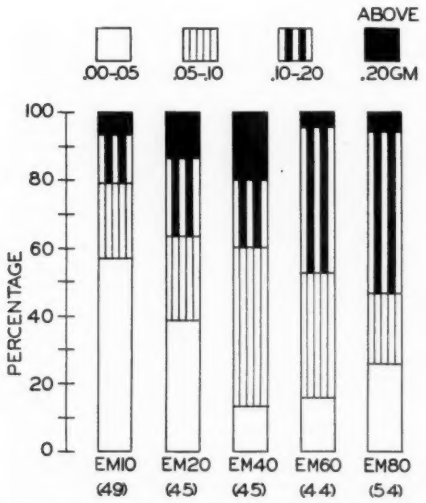

Chart 5.—Effect of diet on the excretion of protein of the partially nephrectomized rat.

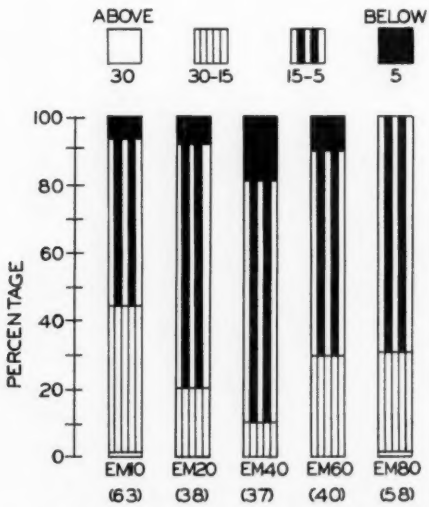

Chart 6.—Effect of diet on the urea ratio of the partially nephrectomized rat.

degree of hypertension and the renal function as measured by the concentration test.

The distribution of the urea ratio values is shown in chart 6. The animals ingesting the EM 40 diet had the largest percentage of ratios below 5. In the dietary group consuming the largest percentage of extracted beef, there was the smallest incidence of animals with renal insufficiency, as judged by the urea ratio.

Effect of Diet on the Urea in the Blood and the Urine.—The adjusted curves and their formulas, obtained by procedures previously described,[2] showing the effect of extracted meat diets on the amount of urea in the blood and the urine in relation to the urea ratio of partially nephrectomized and of control rats are shown in chart 7.

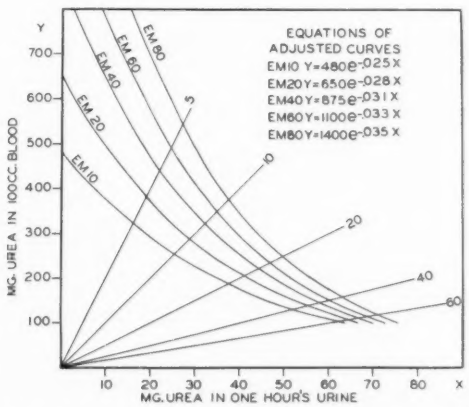

Chart 7.—Relation of the adjusted curves for the urea in the blood and the urine.

In these experiments the unadjusted and adjusted curves are practically identical for all dietary groups.

When the concentrations of the urea in the blood and the urine are compared at any given urea ratio, the influence of diet is strikingly shown. Since urea is given by mouth in definite amounts for the determination of the urea ratio, it is obvious that the retention of urea in marked renal insufficiency represents a cumulative effect of ingested and metabolic urea. It has been frequently noted that animals die shortly after the urea clearance test if the blood urea exceeds 800 mg. of urea per hundred cubic centimeters of blood.

2. Ludewig, S.; Williams, E. T. R., and Chanutin, A.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: VII. The Relationship of Urine Urea, Blood Urea and Urea (Addis) Ratio in Rats on Whole Dried Meat Diets, Arch. Int. Med. **58**:89 (July) 1936.

An analysis of the effect of diet on the concentration of urea in the blood at any given ratio in percentage of mean normal is shown in chart 8. The curves presented were drawn according to formulas derived from the exponential equations for adjusted curves for urea in the blood and the urine in chart 7. No significant difference in the concentration of urea in the blood is noted until the urea ratio reaches a level of about 15. As renal insufficiency becomes more severe, the differences in the concentration is greater between the various dietary groups. The curves for the animals fed the EM 40, the EM 60 and the EM 80 diet do not reach the zero urea ratio line at a level of 800 mg. of urea per hundred cubic centimeters of blood, which is in striking contrast to similar curves obtained for animals ingesting diets containing dried whole meat.

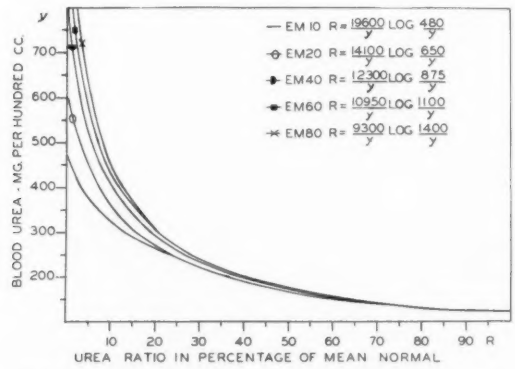
y
BLOOD UREA - MG. PER HUNDRED C.C.
700
600
500
400
300
200
EM 10 R = 19600/y LOG 480/y
EM20 R = 14100/y LOG 650/y
EM40 R = 12300/y LOG 875/y
EM60 R = 10950/y LOG 1100/y
EM80 R = 9300/y LOG 1400/y
10 20 30 40 50 60 70 80 90 R
UREA RATIO IN PERCENTAGE OF MEAN NORMAL

Chart 8.—Relation between the concentration of urea in the blood and the urea ratio in percentage of the mean normal value.

SUMMARY

The effect of feeding diets containing various percentages (10, 20, 40, 60 and 80) of dried extracted meat to intact, unilaterally and partially nephrectomized rats has been studied.

Data showing the effects of these diets on renal hypertrophy, renal function and blood pressure of intact and unilaterally nephrectomized rats are presented. The blood pressure and $\frac{\text{heart weight}}{\text{surface area}}$ remained constant, the $\frac{\text{kidney weight}}{\text{surface area}}$ ratio increased progressively and the $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratio was fairly constant for the intact rats.

The following observations were made on the partially nephrectomized rats:

The incidence of hypertension was high for all groups except those fed the diet containing 80 per cent dried extracted meat. The correlation between $\frac{\text{heart weight}}{\text{surface area}}$ ratios and blood pressure was low for groups ingesting 60 and 80 per cent extracted meat.

The total solids of the kidneys per unit of surface area increased progressively with increased ingestion of protein.

The urinary volumes during a concentration test were smallest for the rats fed the EM 10 diet and greatest for those fed the EM 40 diet. The greatest incidence of low specific gravities was obtained for groups on the diets containing the higher amounts of protein (40, 60 and 80 per cent). Proteinuria was most marked in those fed the EM 40 diet. According to the results of the concentration test, the most marked changes in renal function were noted in rats on the EM 40 diet.

Renal insufficiency, as judged by the urea clearance test, was most marked in the group fed the EM 40 diet and least marked in the group fed the EM 80 diet. Curves showing the relation of diet to the urea in the blood and the urine demonstrate that extremely high concentrations of urea in the blood are associated with low urea ratios.

INTRACEREBRAL CARCINOMATOUS METASTASES

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NEW YORK

There are apparently several ways by which carcinoma may metastasize to the central nervous system. Briefly, these are: (1) by direct extension (along nerve sheaths, by bony invasion or from the meninges); (2) through the lymphatic vessels, usually in retrograde growth, and (3) via the blood stream, as carcinomatous emboli. The different routes of invasion result in different pathologic [1] and clinical pictures.

Direct extension may be from a nearby primary focus, as in the case of carcinoma of the nasopharynx, or from a distant focus preceded by metastasis to a nearby structure, as in the case of carcinoma metastatic to the skull from the thyroid or the prostate. The resultant clinical picture is a combination of the symptoms produced by the structures primarily involved and those produced by the later growth into the central nervous system. Metastasis by the lymphatic route results usually in so-called meningitis carcinomatosa, with the well known picture of diffuse meningeal and encephalic disturbance. This syndrome has been described by a number of writers, including Schwarz and Bertels,[2] Panchontoni,[3] Boyd,[4] Lewis,[5] Fried [6] and Cornwall.[7] The

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Read in part at a meeting of the Neurological Society of Rhode Island, Providence, R. I., April 12, 1937.

1. Winkelman, N. W., and Eckel, J. L.: Metastatic Carcinoma of the Central Nervous System, J. Nerv. & Ment. Dis. **66**:1-14 (July); 133-148 (Aug.) 1927.

2. Schwarz, E., and Bertels, A.: Ueber "Meningitis" carcinomatosa, Deutsche Ztschr. f. Nervenh. **42**:85-94, 1911.

3. Panchontoni, D.: Ueber diffuse Karzinomatose der weichen Hirnhäute, Arch. f. Psychiat. **49**:396-405, 1912.

4. Boyd, W.: Diffuse Tumors of the Meninges, Am. J. Path. **1**:583-593 (Nov.) 1925.

5. Lewis, N. D. C.: An Unusual Manifestation of Metastatic Miliary Carcinomatosis of the Central Nervous System, Am. J. Psychiat. **5**:171-187 (Oct.) 1925.

6. Fried, B. M.: Sarcomatosis of the Brain, Arch. Neurol. & Psychiat. **15**: 205-217 (Feb.) 1926.

7. Cornwall, L. H.: Metastatic Meningo-Encephalic Carcinomatosis Without Tumefaction, Arch. Neurol. & Psychiat. **17**:466-470 (April) 1927.

brain may be invaded directly from this diffuse focus, but the symptoms are overshadowed by the diffuse meningeal and encephalic involvement. The blood stream seems to be the most frequent route of carcinomatous metastasis to the central nervous system. In this type of metastasis the lesions develop within the neural parenchyma. Depending on the number and location of the metastatic nodules, the clinical picture may be that of a tumor of the brain or that of a diffuse cerebral disease. It is the latter type of metastatic cerebral disease with which we are concerned in this communication.

The clinical diagnosis of cerebral metastasis is usually easily established when the patient is known to have a primary carcinomatous tumor. When the history, symptoms or signs of primary carcinoma are lacking the diagnosis may be difficult to make and may be established only after a cranial operation. A search for the primary tumor then leads to its discovery, and its location is most commonly in the lungs. In some cases the diagnosis is established at the autopsy table.[8] Common incorrect clinical diagnoses are primary tumor of the brain, cerebral hemorrhage or thrombosis, encephalitis, abscess of the brain and, in the earlier stages of the illness, psychoneurosis or psychosis.

Our purpose in this paper is to describe the clinical features of 100 cases of intracerebral carcinomatous metastases studied at the Neurological Institute of New York and the Presbyterian Hospital and the pathologic features in 34 of these cases in which autopsy was performed, as studied in the departments of neuropathology of these two hospitals. We have also attempted to compare the features in our group of cases with some of those recorded in the literature. We have limited our study to cases in which the tumor has spread, presumably by way of the blood stream, to involve the parenchyma of the brain and have omitted those in which metastasis has occurred by direct extension or by the lymphatic vessels to involve the bones of the skull or the meninges primarily.

FREQUENCY

There are numerous reports of cerebral metastatic carcinomatous tumors in the literature, and since these reports come from varied sources one may conclude that the disease occurs rather commonly. Statistics from a hospital specializing in the treatment of neurologic

8. Ferguson, F. R., and Rees, W. E.: Cerebro-Spinal Metastases from Unsuspected Pulmonary Carcinoma, Lancet **1**:738-744 (April 5) 1930. Dickson, W. E. C., and Worster-Drought, C.: Multiple Metastatic Tumours in the Brain Arising from Primary Bronchial Carcinoma, J. Neurol. & Psychopath. **16**:289-320 (April) 1936.

diseases are not a true index of the frequency of metastatic tumors but provide an index of their frequency in comparison with that of other tumors of the brain. Operative statistics alone are of little value in such a study. Cushing,[9] in the report of 2,000 cases of tumor of the brain in which the diagnosis was neurosurgically verified, stated that 65, or 3.2 per cent, of the tumors were metastatic but explained that this relatively low incidence was due to the surgeon's reluctance to operate on metastatic growths. In his series, 48 of the 65 metastatic tumors were carcinomatous. Elkington,[10] in his studies of the records of the National Hospital, Queen Square, London, England, found that in sixteen years (1918-1933) there were 805 cases of tumor of the brain in which the diagnosis was histologically verified; and 72, or 9 per cent, of the growths were metastatic. Garland and Armitage,[11] in 264 autopsies on patients who died of cerebral tumor in the Leeds General Infirmary, Leeds, England, found that 12.8 per cent of the tumors were metastatic. Elkington [10] stated that it is reasonable to assume that not less than 20 per cent of all tumors of the brain are metastatic. Roger and Paillas [12] found that metastatic tumors constitute 10 per cent of all cerebral tumors seen at the Neurological Clinic at Marseilles, France. Shelden,[13] in a report of cases from the Mayo Clinic, estimated that 5 per cent of all tumors of the brain studied there are metastatic. He concluded, however, that the percentage may well be higher than this. Bailey [14] estimated from his study of intracranial tumors that metastatic tumors constitute 33 per cent of all tumors of the brain and from the neurosurgical statistics, that they form about 4 per cent. He concluded that both estimates are wrong, for they probably comprise less than 33 per cent of all tumors and more than 4 per cent as verified after craniotomy. We feel that

9. Cushing, H.: Intracranial Tumours: Notes upon a Series of Two Thousand Verified Cases with Surgical-Mortality Percentages Pertaining Thereto, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

10. Elkington, J. St. C.: Metastatic Tumours of the Brain, Proc. Roy. Soc. Med. **28**:1080-1096 (June) 1935.

11. Garland, H. G., and Armitage, G.: Intracranial Tuberculoma, J. Path. & Bact. **37**:461-471 (Nov.) 1933.

12. Roger, H., and Paillas, J. E.: Les tumeurs cérébrales métastatiques: Etude clinique, Presse méd. **42**:2093-2096 (Dec. 29) 1934.

13. Shelden, W. D.: Secondary Tumors of the Brain, J. A. M. A. **87**:650-654 (Aug. 28) 1926.

14. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933, chap. 17, pp. 348-368.

statistics from the Neurological Institute would add little but confusion to the varying data, but we believe that the actual incidence of metastatic cerebral tumors is somewhere between 10 and 20 per cent of all tumors of the brain.

CEREBRAL METASTASIS IN RELATION TO MALIGNANT DISEASE

Statistics, to be of any value in determining the relation of cerebral metastases to primary carcinoma elsewhere in the body, must come from large series of autopsies. Rau [15] observed cerebral metastases in 3.2 per cent of 851 cases of carcinoma, and Krasting [16] in 4.7 per cent of 817 cases. Krasting stated that intracranial metastases follow 18 per cent of all primary carcinomas, this percentage being based on his own statistics and those of Starr, Guilt and Gallavardin and Varay.

In a study of the statistics on primary bronchogenic carcinoma a much higher percentage of metastases is found. Thus, Fried and Buckley,[17] in a study of 38 cases of proved primary bronchogenic carcinoma, observed pathologically verified metastases in the brain in 15 cases (39.2 per cent). Dosquet [18] of 105 cases of bronchial carcinoma observed cerebral metastases in 31 per cent. Seyfarth,[19] on the other hand, observed metastasis to the brain in only 9.7 per cent of 309 cases. Davison and Horwitz [20] found 11 per cent in which primary carcinoma in the lungs involved the central nervous system. In 6 cases in which autopsy was done there was cerebral involvement. We feel that our cases could add little, if anything, to these facts.

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15. Rau, W.: Eine vergleichende Statistik der in 5 Kriegsjahren (1914-1919) und 5 Friedensjahren (1909-1914) sezierten Fälle von Krebs und anderen malignen Tumoren am pathologischen Institut des Stadtkrankenhauses Dresden-Friedrichstadt, Ztschr. f. Krebsforsch. **18**:141-170, 1921.

16. Krasting, K.: Beitrag zur Statistik und Kasuistik metastatischer Tumoren, besonders der Carcinommetastasen im Zentralnervensystem (auf Grund von 12730 Sektionen der pathologisch-anatomischen Anstalt Basel), Ztschr. f. Krebsforsch. **4**:315-379, 1906.

17. Fried, B. M., and Buckley, R. C.: Primary Carcinoma of the Lungs: IV. Intracranial Metastases, Arch. Path. **9**:483-527 (Feb.) 1930.

18. Dosquet, H.: Ueber die Metastasenbildung bei primären Lungen- und Bronchialkrebsen, Virchows Arch. f. path. Anat. **234**:481-484, 1921.

19. Seyfarth, C.: Lungenkarzinome in Leipzig, Deutsche med. Wchnschr. **50**: 1497-1499 (Oct.) 1924.

20. Davison, C., and Horwitz, W. A.: Primary Carcinoma of the Lungs with Metastases to the Central Nervous System, Arch. Int. Med. **46**:680-704 (Oct.) 1930.

SITE OF PRIMARY GROWTH

The sites of the primary growth in our group of 100 cases are shown in the following tabulation.

Site	No. of Cases, or Percentage
Bronchus	42
Breast	23
Stomach	3
Intestine	3
Colon	1
Rectum	1
Ovaries	1
Uterus	1
Kidneys	2
Penis	1
Adrenal glands	2
Thyroid	2
Scalp	1
Skin of finger	1
Undetermined	16
Total	100

It is evident that the great majority (65 per cent) of cerebral metastases have their origin either in the lung or in the breast. This percentage may well be greater than that indicated, as the primary site was undetermined in 16 per cent of the cases.

The pulmonary origin of the primary growth in 42 per cent of our cases is in agreement with the data of Meagher and Eisenhardt,[21] who found that 35 per cent of metastases in their cases originated in the lung. In the 72 cases reported from the National Hospital[10] 33.3 per cent of the metastases originated in the bronchus, whereas Grant,[22] in 43 cases, found a bronchial origin in only 13.5 per cent. Other reports show variation in the percentage frequency of the bronchi as a primary site, but most of them place it between 30 and 50 per cent.

In our series of 100 cases 23 per cent of metastases originated in the breast. This conforms with the statistics of others: e. g., Meagher and Eisenhardt, 25 per cent; Elkington, 18 per cent, and Grant, 31.3 per cent.

Other sources of the primary growth appear in the published reports in about the same percentage relation as is shown in table 1.

21. Meagher, R., and Eisenhardt, L.: Intracranial Carcinomatous Metastases with Note on Relation of Carcinoma and Tubercle, Ann. Surg. **93**:132-140 (Jan.) 1931.

22. Grant, F. C.: Concerning Intracranial Malignant Metastases: Their Frequency and the Value of Surgery in Their Treatment, Ann. Surg. **84**:635-646 (Nov.) 1926.

In our series the left breast was primarily involved in 12 and the right breast in 11 cases. The left bronchus was the primary site in 14 and the right in 18, of the cases in which a definite laterality could be determined.

INCIDENCE

Age.—The incidence according to age in our series of 100 cases is shown in the following tabulation.

Age, Years	No. of Cases
10-20	1
20-30	4
30-40	22
40-50	34
50-60	29
60-70	9
70-80	1

Average age, 44.6

The youngest patient in the group was a girl 12 years of age, with a primary carcinoma of the thyroid. The oldest patient was 70, with metastasis presumably from the gastrointestinal tract. The average age of 44.6 years compares with Elkington's average of 47 years.

It is of interest to note that in our series 27, or 27 per cent, of the patients were less than 40 years of age.

Sex.—There were 54 males and 46 females in the series. In the group of patients with the primary tumor in the lung it is of interest to note that there were 32 males, as compared with 10 females.

DURATION OF SYMPTOMS

The duration of neurologic symptoms prior to entrance to the hospital varied from a few days to one and a half years. In 84 of the 100 cases symptoms were present for less than five months. In 6 cases symptoms were present for one year or more. In 2 instances neurologic symptoms were lacking. The following tabulation shows the duration of symptoms before the patients were admitted to the hospital.

Duration	No. of Cases
1- 5 weeks	30
5-10 weeks	30
10-20 weeks	24
20-30 weeks	5
30-40 weeks	3
12 months	4
14 months	1
18 months	1
No symptoms	2

Cerebral symptoms of a primary tumor of the brain are usually of much longer duration prior to hospitalization than were the symptoms in this group of metastatic tumors. Glioblastoma multiforme is, however, an exception.[23]

Of the 6 cases in which symptoms were present for one year or more, it was observed that there were metastases from the lung in 3, from the breast in 1, from the gastrointestinal tract in 1 and from an undetermined source in 1.

DURATION OF LIFE

The duration of life in this group is measured as from the occurrence of the first neurologic symptom to the time of death. In some cases this has not been determined, because we were unable to ascertain whether or when death occurred. In the group of 34 cases in which autopsy was performed in our own laboratories the time varied between three weeks and fifteen months and averaged three and six-tenths months. In an additional group of 40 patients discharged from the hospital, who later died, we found the average duration of life to be six and four-tenths months. In this group death followed the initial cerebral symptom in periods ranging from two weeks to twenty-five months. The case of the 1 patient who survived for twenty-five months after signs of cerebral metastasis from a primary tumor of the breast is unusual. Of the remainder of the group, 7 survived for approximately fifteen months.

In Elkington's series the average duration of life after the onset of cerebral symptoms was six and three-tenths months, which is, strangely, in close accordance with the average of six and four-tenths months for our patients who died after leaving the hospital.

MODE OF ONSET

The initial symptom referable to intracranial disease appeared in one of three general manners; these are classified as sudden, rapid or gradual. The onset in 5 cases did not fit into this classification. In 2 of these there were no neurologic symptoms, and in the 3 others we were unable to classify the mode of onset because of confusing statements in the case history.

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23. Globus, J. H., and Selinsky, H.: Metastatic Tumors of the Brain: A Clinical Study of Twelve Cases with Necropsy, Arch. Neurol. & Psychiat. **17**:481-513 (April) 1927.

In 36 of the 100 cases the onset of symptoms was sudden. The first symptoms were as follows:

Symptom	No. of Cases
Convulsive seizures	10
General	7
Jacksonian	3
Headache, vertigo and vomiting	8
Headache	5
Hemiplegia or hemiparesis	3
Aphasia	2
Vertigo	2
Mental disorder	1
Headache and diplopia	1
Headache and hemiplegia	1
Headache and dysarthria	1
Scotomas	1

The intracranial symptoms developed rapidly in 42 cases. In this group the first symptoms were:

Symptom	No. of Cases
Headache	30
Mental disturbances	5
Hemiparesis	2
Monoparesis	1
Sensory disturbances	1
Diplopia	1
Diplopia and tinnitus	1
Vomiting	1

A gradual onset was recorded in 17 cases. The symptoms were at first mild and were slower in their progressive development than in the other two groups. The first symptoms were:

Symptom	No. of Cases
Headache	10
Mental disturbances	3
Failing vision	2
Hemiparesis	1
Monoparesis	1

Thus, the manner of onset of intracranial symptoms in at least 78 cases appears to be different from that observed in cases of other tumors of the brain, except glioblastoma multiforme. In the cases of sudden onset there were manifestations similar to those associated with cerebral vascular accidents. The mode of onset in these cases certainly simulates that seen in patients in whom a non-neoplastic embolus suddenly lodges in a cerebral vessel.

SYMPTOMS

General Symptoms.—Forty of the 100 patients appeared to be in good general health. In this group the signs so often suggestive of malignant tumor were lacking. There were indications of some weakness and increasing fatigability, associated with a slight loss of weight, in 31 of the remaining patients. In 29 there were pronounced cachexia and signs of a debilitating disease. Fever was an outstanding symptom in only 2 cases.

Headache.—Headache of varying degrees was an outstanding symptom in 83 of the 100 cases. In 49 instances it was associated with various degrees of papilledema. In 34 there was headache without associated papilledema. Seventeen patients did not complain of headache, and none of these had papilledema.

The headache was frequently well localized and commonly paroxysmal. In many cases it was severe and was associated with vomiting. In most cases it was not relieved by the usual dehydration methods or by the use of drugs of such strength as one hesitates to prescribe for the usual headache due to tumor of the brain. The headache, for which little relief was offered, was one of the most distressing features of the disease to both patient and physician.

Vomiting.—Vomiting occurred during some stage of the illness of 59 patients. It was frequently associated with periodic headache or vertigo and was often projectile.

Mental Alterations.—There were mental alterations of varying degrees in 50 of the 100 cases. In this group there were true mental alterations during the earlier part of the illness. The change was of mild degree in 29 and was characterized by slowness in mental reaction, faulty memory, mild degrees of depression, emotional instability, irritability, loss of interest and reduced powers of attention.

Pronounced alterations in mentality were observed in 21 patients. In these, in addition to greater degrees of the symptoms aforementioned, there was usually profound mental confusion. Patients of this type required constant nursing. They were incontinent, required spoon feeding and often had to be restrained in bed. Hallucinations were not infrequent. At times the confusional states cleared so that the patients were perfectly rational, with good insight. It seems plausible that the mental symptoms, at least in some instances, were intensified by general systemic toxemia, such as one sees in patients with carcinoma without metastases to the brain. The incidence (50 per cent) of mental symptoms appears to be higher than in patients with nonmetastatic tumors.

In the remaining group of 50 patients, considered to be without mental disturbances, there were some who were somnolent or stuporous for four to seven days before death.

Convulsive Seizures.—Twenty of the 100 patients had one or more convulsive seizures. Focal motor seizures without loss of consciousness

were present in 9 cases and focal sensory seizures in 2. Generalized convulsive seizures with loss of consciousness occurred in 7 patients. One had both general and focal seizures. In 1 patient there was periodic loss of consciousness, with an aura consisting of auditory, uncinate and gustatory phenomena and without any actual motor activity.

Autopsies were performed on 6 of these patients. Autopsy revealed a single metastatic nodule in the motor arm area of the left precentral gyrus of a patient who had previously had clonic movements of the right arm. Periodic sensory disturbances on the left side had been observed in 1 patient, and these were later replaced by motor convulsions. At autopsy one metastatic tumor nodule was seen in the right postcentral and precentral rolandic convolutions. Two patients had generalized convulsive seizures, and multiple nodules were observed in the brain at autopsy. Two other patients had unilateral seizures, and multiple nodules were seen at autopsy.

The convulsive phenomena outlined appeared to correspond with lesions in the cerebral areas, which was to be expected. In 2 cases they localized single metastatic nodules; in 4 others they localized only one of many nodules.

SIGNS REFERABLE TO CEREBRAL DESTRUCTION OR DIRECT COMPRESSION

There was clinical evidence of either destruction or direct compression of brain tissue in 68 of the 100 cases. The motor components were most commonly involved. The following disorders were observed in 68 patients, several of whom had more than one of the signs enumerated:

Symptom	No. of Patients
Hemiplegia	22
Monoplegia	5
Paraplegia	1
Quadriplegia	1
Slight hemiparesis	5
Slight monoparesis	1
Local sensory disturbances	8
Ataxia	16
Aphasia	21
Apraxia	1
Deafness	2
Dysphagia	1
Dysphonia	1
Dysarthria	1
Trigeminal pain	2
Trigeminal anesthesia	3
Facial paralysis (peripheral)	2
Hemianopia	5
Urinary disturbances	2

The signs outlined were usually of marked degree and showed no evidence of improvement; they were more apt to become progressively worse. The exception to this was the peripheral facial paralysis, which cleared up in about ten days. Patients with hemiplegia often had monoplegia first. The ataxia was frequently truncal. Aphasia and hemiplegia occurred commonly in combination in the same patient. Hemianopia, when present, was usually homonymous.

VISUAL SYMPTOMS REFERABLE TO INCREASED INTRACRANIAL PRESSURE

Thirty-five patients showed visual symptoms referable to increased intracranial pressure, although many, such as blurring of vision, were mild. Diplopia, usually transient, was a prominent symptom in 10 cases and was apparently due to general pressure on either one or both of the abducens nerves intracranially, so that paresis of the lateral rectus muscle resulted. Seventeen of the group complained of blurred vision, which appeared to be caused by papilledema. Two patients complained of photophobia. Amblyopia was present in 1 patient despite absence of papilledema or atrophy of the optic nerve. A single cerebellar metastasis, observed at autopsy, did not appear to explain this condition.

MENINGEAL IRRITATION

Some writers have recorded meningeal irritation as a common symptom. We observed it in 7 patients. It was evidenced by slight nuchal rigidity and a subjective sense of stiffness of the cervical muscles, associated with severe headache.

PAPILLEDEMA

Well defined papilledema of measurable degree, often accompanied by retinal hemorrhages, was seen in 31 of the 100 patients. In 40 additional patients the heads of the optic nerves were hazy or blurred. The opinions of different observers varied as to whether this represented beginning papilledema. The optic fundi appeared normal in the remaining 29 cases. Secondary atrophy of the optic nerve did not develop because of the relatively short duration of the papilledema prior to death.

SYMPTOMS REFERABLE TO THE PRIMARY GROWTH

The 23 patients with tumors of the breast all had shown definite indications of the condition, and in all instances a mastectomy had been performed. There were definite signs of a primary malignant tumor in 18 additional patients, and in the cases of many of these previous histologic studies had established the diagnosis. Symptoms suggestive

of a primary malignant tumor were present in 9 cases. These included slight cough, pain in the chest, hemoptysis and gastrointestinal disturbances. In 34 cases symptoms referable to a primary malignant tumor were lacking or were not elicited. Cases of carcinoma of the lung formed the greater part of the last group, and, as has been emphasized by Bunts,[24] the intracranial disease was the earliest evidence of the pulmonary condition. In 16 cases (table 1) the original site of the malignant growth was not determined.

Only 2 of the 42 primary bronchial growths produced signs which pointed definitely to the source. These signs were fever, chills, cough and hemoptysis. In 10 additional cases there were suggestive symptoms, such as slight cough with or without hemoptysis, and in a few there was pain in the chest. Thirty of the primary bronchial growths failed to produce symptoms. Elkington [10] observed symptoms referable to the chest in 7 of his 9 cases of bronchogenic carcinoma. These symptoms were not severe enough for the patients to consult a physician, but were elicited on questioning after the onset of cerebral symptoms.

CEREBROSPINAL FLUID

A study of the cerebrospinal fluid was made in 54 of the 100 cases and of the ventricular fluid in 5 additional ones. In 38 (70.3 per cent) of the 54 cases the spinal fluid was abnormal, with regard chiefly to an increase in the total protein content and the globulin reaction and in a few specimens to an increase in the cellular content. A positive Wassermann reaction was obtained in the stronger dilutions in 3 specimens. Only 1 such reaction was associated with a positive Wassermann reaction of the blood. Three of the 5 specimens of ventricular fluid were abnormal in the same respect as the spinal fluid.

The spinal manometric pressure was recorded in 18 instances, and in these it was greater than the top normal value of 180 mm. of water in 7 cases. Slight leukocytosis was found in 7 of the 54 specimens, and for these the cell counts were recorded as 55, 50, 48, 17, 15, 12 and 11 per cubic millimeter, respectively. Lymphocytes predominated in all. This cellular increase in the spinal fluid occurs with about the same frequency as in cases of primary cerebral neoplasm, according to a previous study by one of us (C. C. H.)[25] of 186 such cases.

The total protein content was increased in 38 specimens and measured between 56 and 241 mg. per hundred cubic centimeters. The

24. Bunts, A. T.: Intracranial Metastasis as Earliest Evidence of Carcinoma of the Lung, Cleveland Clin. Quart. **3**:234-241 (July) 1936.

25. Hare, C. C.: The Cerebrospinal Fluid Obtained by Lumbar and by Ventricular Puncture in Tumors of the Brain, Bull. Neurol. Inst. New York **4**:64-90 (March) 1935.

globulin reaction in a like number of specimens was increased to from 1 to 3 plus.

ROENTGEN STUDY OF THE SKULL

Stereoscopic roentgenograms of the skull were taken in 91 of the 100 cases. They appeared normal in all respects in 40 and abnormal in 51. Metastases to the bones of the skull were seen in 15 cases. A calcified pineal gland was displaced in 24 additional cases. Erosion of the clinoid processes or the dorsum of the sella turcica was evidence of increased intracranial pressure in 22 cases. In many of the last-mentioned group the pineal gland was also displaced. Calcification in a tumor mass was observed in the roentgenogram of the skull in 1 case.

Encephalographic studies were made in 10 cases, and in 8 of these there were abnormalities indicative of a tumor. Ventriculograms were taken in 9 additional cases. Six were abnormal but lacked evidence for a positive diagnosis of tumor or for localization of the growth. In the remaining 3 there was definite localization of a tumor.

The erosion of portions of the sella turcica in 25 cases is of interest. In 10 of these the period elapsing between the first neurologic symptom and the roentgenographic study of the skull was less than three months. The changes in the sella turcica in these 10 cases were slight, but were considered definitely abnormal.

The calcification observed in the tumor in 1 case is of interest, for usually the metastatic mass is present for too short a time to permit such a change. In this particular case a mammary carcinoma had been removed five years previously, and cerebral symptoms were noted only two months prior to roentgen study of the skull. At autopsy three tumor masses were observed in the brain, one corresponding in location with the calcification seen on the roentgenograms. All three masses contained areas of caseous degenerated tissue.

ROENTGEN STUDY OF THE CHEST

Roentgenograms of the chest were taken in 35 of the 42 cases in which a bronchogenic carcinoma was diagnosed at autopsy. A roentgen diagnosis of primary tumor of the lung was made in 27 of the 35 cases. In 7 other cases the roentgenologist reported changes in the lungs suggestive of an infectious process, including enlargement of the peribronchial lymph nodes in 1 instance and pleural effusion in another. In only 1 case were the roentgenograms entirely normal. Not infrequently the primary bronchogenic carcinoma is so small that even at autopsy it is seen only after prolonged search. It may originate in a secondary or tertiary bronchial tube.

Roentgenograms of the chest were taken in 20 of the 23 cases of primary carcinoma of the breast. Metastases to the lung were seen in

14 of the 20 cases. A shadow suggestive of an aneurysm appeared in the roentgenograms of 1 patient. Permission for autopsy was not obtained in this case. In 2 cases the lungs appeared entirely free of metastases.

Roentgenograms of the chest were taken in 5 of the 8 cases of tumor primary in the gastrointestinal tract; in only 1 were there signs of metastasis, and that was from the colon.

Roentgenograms of the chest in the cases of primary growths in the ovaries or adrenal glands showed nothing abnormal. Pulmonary metastases were present in each of the cases of primary carcinoma of the penis or uterus. One of the 2 renal tumors metastasized to the lung, as did 1 of the 2 carcinomas of the thyroid.

Of the 16 cases in which the site of the primary growth was undetermined, roentgenograms of the chest were taken in 8; they were normal or showed an old infectious process. In 1 a tumor of the lung was suspected.

DIAGNOSIS

The diagnosis is simple in cases in which there are a known primary carcinoma of the breast and later signs indicative of a cerebral neoplasm. The metastases may occur a number of years after surgical or roentgen treatment of the mammary tumor. In 22 of our 23 cases of metastatic carcinoma of the breast, the interval between the mastectomy and the first neurologic symptom averaged twenty-five months. The shortest interval was four months and the longest six years, except in 1 instance, in which the neurologic signs preceded the mastectomy. The metastases occurred despite the fact that most of the mastectomies were of the radical type and were followed by roentgen therapy. Unfortunately, no complete data are available regarding the duration and amount of the roentgen therapy and the extent of the operative procedures. Frequently the metastases pass first to the lungs and may be seen there in roentgenograms. In all the cases in our series the correct diagnosis was made.

When the primary growth is in the bronchial tissue and there are signs of a tumor of the brain an incorrect diagnosis is common. This results either from failure to elicit a history of any bronchial disturbance or from failure of symptoms of such a disturbance to develop. Roentgen studies of the chest are therefore often omitted, and clinical examination of the chest rarely aids in diagnosis of a small growth. It is therefore not known that a bronchogenic carcinoma is present, and all efforts are aimed at determining the cause of the presenting cerebral disturbances. This is then often determined to be a primary tumor of the brain, usually of gliomatous origin. It may be only after the surgeon has performed a craniotomy and has examined a specimen of the tumor tissue histologically that the true nature of the disease is known.

Roentgenograms of the chest then usually reveal a tumor arising from a bronchus. In other cases in which the surgeon fails to find the tumor tissue in the brain the diagnosis may be made only at the autopsy table. Probably in many instances the correct diagnosis is never established.

In many cases of undetermined bronchogenic carcinoma the cerebral disturbances may be diagnosed as resulting from cerebral thrombosis or hemorrhage, abscess of the brain, subdural hematoma, cerebral aneurysm, encephalitis or cerebral arteriosclerosis. In our series of cases such a diagnosis was commonly made by one or more of the many physicians who examined each patient clinically.

In cases in which there is a primary growth elsewhere than in the bronchial tree there are usually indications which lead to the diagnosis of carcinoma before cerebral metastases occur.

PATHOLOGIC STUDIES

Autopsy studies were made in our own pathologic laboratories in 34 of the 100 cases. In most cases a complete autopsy was permitted; in others the contents of the cranial cavity only were examined. In 6 additional cases autopsy reports confirming the presence of cerebral carcinomatous metastases were received from laboratories of other hospitals. Data from these reports are not included in the following sections.

Gross Appearance of the Brain.—The outstanding feature was the asymmetry of the cerebral or cerebellar hemispheres with distortion of the associated structures. These changes were not extensive but were localized to the regions invaded by the carcinoma. In most cases the ventricular systems were involved in the distortion. The cerebral gyri were frequently flattened and the sulci narrowed, and the entire brain had a swollen, edematous appearance. Tumor masses extended to the cortical surface in only 2 brains. A distinct herniation of the cerebellar structures into the foramen magnum was seen in 3 cases.

Number of Tumors.—Multiple tumors were present in 20 brains and single tumors in 14.

Position of Tumors.—The cerebrum was involved in 26, the cerebellum in 16, the brain stem in 6 and the pituitary gland in 2 cases. Single nodules were observed in one cerebellar hemisphere in 5 cases and in one cerebral hemisphere in 8 cases. A single metastatic nodule was seen within the medulla oblongata in 1 case.

Elkington [10] pointed out that these types of tumor invariably involve the brain substance at the junction of the central white and the cortical gray matter. This localization of the metastatic nodules within the parenchyma was observed in the great majority of our cases (fig. 1). Most of the larger tumors seemed to extend into the white rather than the

gray matter. Elkington [10] further pointed out that the junction between white and gray matter is the usual location of metastatic abscesses of the brain. He suggested that the predilection of this area for blood-borne foreign bodies may be due to the breaking up of the pial arterioles into their terminal capillaries at this point.

Appearance of Tumors.—The tumor masses varied greatly in size. As a rule, if large tumors were present they were few. The larger

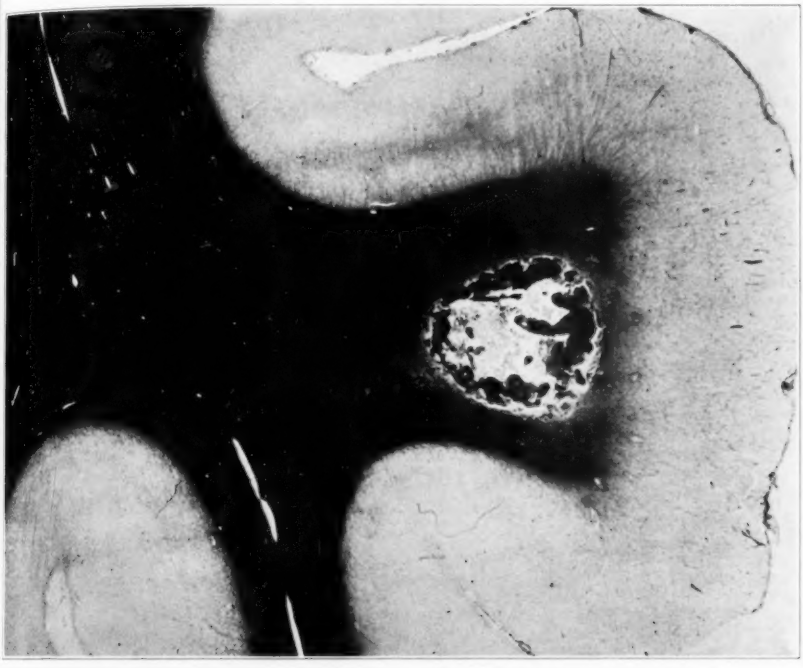

Fig. 1.—Miliary nodule of a carcinoma metastatic to the cerebrum. Note the position of the nodule at the junction of the gray and the white matter. The photomicrograph shows well the destruction of the parenchyma at the site of the lesion. Note the good preservation of the myelin in the vicinity of the metastatic tumor. Pal-Weigert stain; × 12.

masses frequently measured 5 to 10 cm. in diameter. In some brains great numbers of pinhead-sized tumors were present, the brain giving the appearance of having been sprayed with metastases.

The larger tumors were commonly composed of soft degenerated tissue and in some instances were actually cystic. The firmer tumors

were well demarcated, and some shelled out easily from the formaldehyde-hardened brain tissue.

Appearance of Meninges.—The dura was grossly involved by a large tumor in 2 cases. In 1 of these the frontal bone was also eroded. The

Fig. 2.—Reactive astrocytosis at the margins of the metastatic carcinoma nodule in the brain. Cajal stain; × 454.

pia-arachnoid was grossly involved in the vicinity of the underlying tumor in 2 additional cases. No cases of meningeal carcinomatosis were included in our series.

Metastases to Structures Other Than the Brain.—In only 2 of the 20 cases of primary carcinoma of the lung was the brain the sole recipient of metastases. The other structures most commonly involved

were (1) the regional lymph glands, (2) the adrenal glands, (3) other pulmonary areas and (4) the liver. Less commonly affected structures were the ovaries, pancreas, pericardium, diaphragm, long bones, kidneys, spleen and periprostatic tissue. In 3 of the 9 cases of primary tumor

Fig. 3.—Perivascular orientation of the tumor cells. There is no proliferation of the vascular elements. Laidlaw connective tissue stain; × 454.

of the breast there were metastases only to the brain. Other structures commonly involved were (1) the lungs, (2) the liver, (3) the adrenal glands and (4) the pancreas. The structures less frequently involved were the axillary lymph glands (most of them had been previously removed or treated with roentgen rays), heart, stomach, colon, ovaries, kidneys and thyroid.

There were 5 cases in which the primary malignant tumor was not located. Autopsies in 4 of these cases were limited to the head; in the fifth, though the autopsy was complete, there was no evidence of the primary growth or of metastases except in the brain. It seems likely that metastasis originated from a small bronchogenic carcinoma. In a few cases the primary bronchogenic tumor was very small.

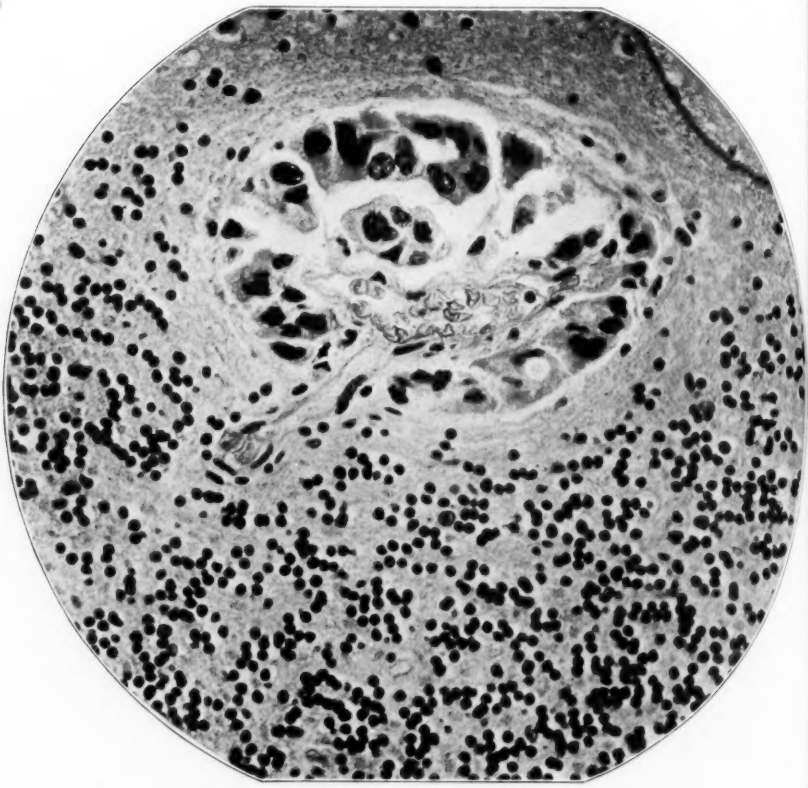

Fig. 4.—Cluster of metastatic carcinoma cells about a capillary of the cerebellum in an invaded area. Hematoxylin and eosin stain; × 384.

In the 1 case of carcinoma primary in the adrenal gland there were metastases to the kidney, lung and lymph glands as well as to the brain. In the case of carcinoma primary in the colon there were metastases to the lung and the cervical vertebrae as well as to the brain.

Microscopic Appearance of Tumors.—The tumor cells of the metastatic nodules in the brain varied, as did the cell type of the primary tumor. In the majority of cases the cell types in the metastases were

identical with those of the primary growth. However, in a few instances the cells of the cerebral metastases showed a definite histologic difference in size and arrangement from those of the primary tumor. The larger tumors showed a considerable degree of degenerative change centrally. At the margins of the nodules small clumps of tumor cells were seen invading the nearby parenchyma about the blood vessels (figs. 3, 4 and

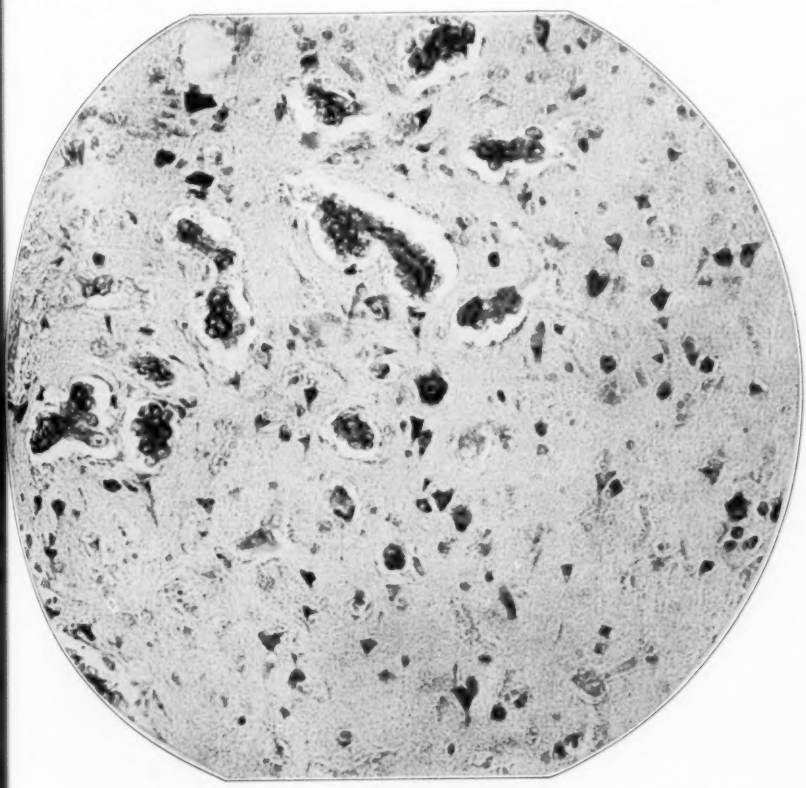

Fig. 5.—Metastatic carcinoma infiltrating the cortex by perivascular growth. Note the degeneration of many ganglion cells between the projecting fingers of tumor tissue and the good preservation of some nerve elements away from the invaded area. Nissl stain; × 192.

5). In a few cases tumor cells were observed within the lumen of the blood vessel. We believe that this tendency of the tumor cells to orient themselves about the blood vessels is one of the most striking features of cerebral metastatic carcinoma.[26]

26. Hassin, G. B., and Singer, H. D.: Histopathology of Cerebral Carcinoma, Arch. Neurol. & Psychiat. **8**:155-170 (Aug.) 1922.

It should be stressed that the invaded brain tissue was totally destroyed and replaced by tumor tissue (fig. 1). This may be important as an explanation of the fact that there is little evidence of increased intracranial pressure in cases of metastatic tumor. Whereas in cases of primary tumor of the brain the infiltration and moderate destruction of parenchyma result in an increase in intracranial contents, in cases

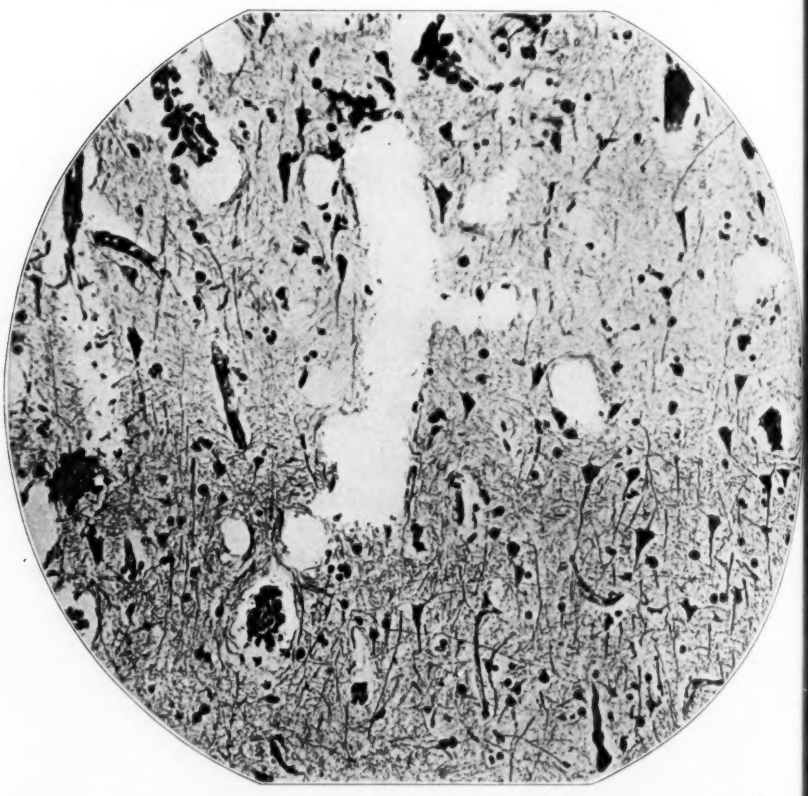

Fig. 6.—Spaces representing the position of the tumor nodules (perivascular). The photomicrograph shows the preservation of neurofibrillae in the heart of the invaded zone, although many are degenerated. The neighboring tissue is well preserved. Bielschowsky stain; × 192.

of metastatic tumor, the complete destruction of the parenchyma and its replacement by neoplastic tissue suggest that there is less increase in intracranial contents, and therefore less increase in intracranial pressure in most cases.

Microscopic Appearance of Surrounding Brain.—At autopsy some of the larger metastatic nodules could be enucleated easily and appeared to be entirely removable. Microscopically, however, tumor cells were seen extending into the surrounding brain tissue in many instances. The greatest change appeared to be the edema of the surrounding brain tissue, with swelling of the glial cells, but for the most part the adjacent parenchyma was well preserved (figs. 5 and 6). In most cases there was a considerable increase in the number of astrocytes in the brain tissue immediately surrounding the tumor (fig. 2). Perivascular infiltration of polymorphonuclear leukocytes and lymphocytes appeared commonly.

TREATMENT

Treatment is directed toward making the patient as comfortable as possible. As has been mentioned, the usual methods of dehydration do not appear to relieve the headache to any great extent. In 3 of our cases relief from headache was obtained for a few weeks by this form of treatment.

Surgically, it does not appear warranted to do more than a subtemporal decompression. There have been numerous reports of relief from headache by this procedure. Nine of the 34 patients in our series were operated on. In 2 cases subtemporal decompression was done with relief from headache, but both patients died in less than two weeks after the operation. A craniotomy was performed in 5 additional cases, death following in 4 instances in less than two weeks. One additional patient was thought to have a subdural hematoma because a trauma to the head precipitated his symptoms. Trephines of the skull and ventriculograms failed to disclose hemorrhage. The patient died seven days later. A ventriculogram was taken of another patient, and his condition became much worse. These few reports seem to indicate that patients with intracranial metastatic tumor do not stand well even the simplest neurosurgical procedures. Seven of the 9 patients operated on died within two weeks after the operation. It seems doubtful, therefore, whether any operative procedure is advisable.

In our series 1 patient with severe headache was relieved by roentgen therapy. This form of treatment may be worth at least a trial.

There is considerable variance of opinion as to operative treatment of patients with carcinomatous metastates, particularly when it is thought that the metastatic lesion in the brain is single. Oldberg [27] has reported 2 cases in which the postoperative period of survival was more than two years and another in which it was eight months. His experience has led him to advocate operation under favorable conditions.

27. Oldberg, E.: Surgical Considerations of Carcinomatous Metastases to Brain, J. A. M. A. **101**:1458-1462 (Nov. 4) 1933.

Fried and Buckley [17] favored operative treatment because it prolonged the lives of 4 of their patients for five months, seven months, two years and seven years, respectively. Five other patients died within two weeks after operation. Cushing,[9] Grant,[22] Elkington,[10] Bunts [24] and others have favored a less radical procedure, such as decompression for relief from intracranial pressure, provided any operative procedure is indicated. In our opinion operation is indicated only for patients suffering pain from an associated increase in intracranial pressure. Decompression may afford temporary palliation of symptoms in such cases and appears to be indicated, provided the general health of the patient is such that at least a few months of life are to be expected. Most of the reports in the literature show that removal of a metastatic nodule from the brain, even though it is single, does not greatly prolong life.

CONCLUSIONS

1. Bronchogenic and mammary carcinoma commonly metastasize to the brain.

2. The primary carcinoma in cases of cerebral metastasis is most commonly in the lung or breast. In our series of 100 cases there were 65 in which the primary tumor was so located.

3. A bronchogenic carcinoma often manifests its effects by cerebral metastasis before there are any pulmonary signs.

4. Carcinoma with cerebral metastases is not uncommon in persons less than 40 years of age. In our series it occurred in 27 of 100 cases.

5. The disease occurs predominantly in male patients, in the ratio 3.2:1, provided the cases of primary carcinoma of the breast are excluded.

6. Symptoms of metastasis are usually of short duration before the patient becomes seriously ill.

7. Gradual onset of intracranial symptoms in cases of metastatic intracerebral carcinoma, according to this study, is infrequent (17 per cent). The onset occurred suddenly in 36 of our 100 cases.

8. Patients with metastatic cerebral tumor do not tolerate surgical procedures well. The average duration of life from the time of the first neurologic symptom until death was three and six-tenths months for the 32 persons who died while under our care. The survival period was much shorter for those who were operated on.

9. Mental alterations may occur. Alterations of varying degree were present in 50 per cent of the patients studied, exclusive of those observed during the few days preceding death.

10. Severe headache may be an outstanding symptom. It may or may not be associated with papilledema.

11. Signs of chronic debilitating disease may be absent. They were lacking in 40 per cent of the cases in this series.

12. Abnormality of the spinal fluid is a prominent finding. It occurred in 70 per cent of the cases in which the spinal fluid was examined.

13. Roentgenographic erosion of the sella turcica may be present. In this series it was not uncommon in spite of the supposedly short duration of the cerebral metastases.

14. Encephalographic and clinical studies may localize one of the metastatic masses, which is usually the largest, and may fail to show the presence of other, smaller nodules.

15. Even after metastasizing to the brain, bronchogenic carcinoma may not appear as such on roentgenograms of the chest.

16. Metastatic cerebral tumors may be single or multiple. Multiple tumors were observed in 20 brains removed at autopsy; single nodules, in the remaining 14 cases.

17. In practically all cases of cerebral metastasis there are metastases to other organs.

18. Cerebral disease in addition to the metastases may be present. In 1 of our cases a cholesteatoma was observed in the cerebellopontile angle at autopsy, and in 3 syphilis of the central nervous system was evidenced by positive Wassermann reactions of the spinal fluid.

19. A primary cerebral neoplasm may be present with a carcinoma elsewhere in the body. We have observed 2 cases, not included in this series, in which a cerebral glioblastoma multiforme was verified pathologically and was associated with a prostatic carcinoma without metastases. Cases in which there were cerebral metastases from the prostate tissue were lacking in our series.

20. Surgical removal of single metastases in a few cases may prolong life for months, or even for several years; such cases, however, form a small percentage of those in which operation is done, most of the patients dying shortly after craniotomy.

21. Subtemporal decompression often relieves the headache and affords great comfort to the patient and his relatives.

22. When craniotomy is to be performed roentgen studies of the chest should be made, regardless of the age of the patient.

Permission to use the autopsy material described in this paper was granted by the department of pathology, Columbia University College of Physicians and Surgeons.

PRIMARY CARCINOMA OF THE LIVER

TUMOR THROMBOSIS OF THE INFERIOR VENA CAVA AND RIGHT AURICLE

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The comparative rarity of primary carcinoma of the liver is shown by the figures of Rowen and Mallory,[1] who found 7 instances of this condition in 6,506 consecutive autopsies. Orth [2] found 4 cases of primary carcinoma of the liver in 258 cases of hepatic cancer and in 713 cases of cancer of all types. Goldzieher and Bokay [3] encountered this disease 18 times in 6,000 necropsies. Hansemann [4] and Rindfleisch [5] concluded from their studies that primary carcinoma of the liver represents about 0.5 per cent of all cancers.

Ewing [6] stated that metastasis occurs infrequently. Of 163 cases of primary carcinoma of the liver studied by Eggel,[7] 46, or 28 per cent, showed no extensions, and in 50, or 30 per cent, metastasis was limited to the branches of the hepatic or the portal veins. The lungs were the most frequent extrahepatic site of metastasis.

The great infrequency with which tumor thrombosis of the inferior vena cava occurs was shown by Simpson.[8] In his study of this condi-

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From the Department of Medicine, the Louisiana State University Medical Center, and the Charity Hospital.

1. Rowen, H. S., and Mallory, J. B.: A Multinucleated Liver Cell Carcinoma, Am. J. Path. **1**:677, 1925.

2. Orth, J.: Lehrbuch der speciellen pathologischen Anatomie, Berlin, A. Hirschwald, 1887, p. 955; cited by Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1931, pp. 721 and 731.

3. Goldzieher, M., and von Bokay, Z.: Der primäre Leberkrebs, Virchows Arch. f. path. Anat. **203**:75, 1911.

4. Hansemann, D.: Ueber den primären Krebs der Leber, Berl. klin. Wchnschr. **27**:353, 1890.

5. von Rindfleisch, H.: Lebercirrhose und gewissen epithelialen Neubildungen der Leber, München. med. Wchnschr. **48**:283, 1901.

6. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1931, pp. 722-723.

7. Eggel, H.: Ueber das primäre Carcinom der Leber, Beitr. z. path. Anat. u. z. allg. Path. **30**:506, 1901.

8. Simpson, W. M.: Tumor-Thrombosis of the Inferior Vena Cava, with Four Additional Cases of Neoplastic Invasion, Ann. Clin. Med. **3**:29, 1924.

tion, he was able to find but 78 cases in the literature up to 1924. In only 7 of this number was the condition due to primary carcinoma of the liver.

The rarity of tumor thrombosis of the inferior vena cava or the right auricle resulting from primary carcinoma of the liver is further shown by my survey of the literature, in which I found reports [9] of 234 cases of primary carcinoma of the liver. In only 6 of this number was there thrombosis of the vena cava or right auricle.[10] In 1 of these cases [10d] the involvement was insufficient to produce any obstruction. In another [10e] the tumor thrombus in the right auricle resulted from direct extension through the diaphragm and wall of the right auricle.

The difficulties encountered in the diagnosis of primary carcinoma of the liver with tumor thrombosis of the inferior vena cava or right auricle or both of sufficient degree to produce obstruction caused me to analyze the 7 cases previously reported by Simpson and the 4 additional cases found in the literature and to report my study of an additional case.

REPORT OF A CASE

C. W., a Negro aged 35, a farm laborer, was admitted to the medical service of the Charity Hospital on Sept. 6, 1936. His complaints were pain in the back and swelling of the extremities. Five weeks before admission, his left ankle began

9. Clawson, B. J., and Cabot, V. S.: Primary Carcinoma of the Liver, J. A. M. A. **80**:909 (March 31) 1923. Griffith, J. P. C.: Primary Carcinoma of the Liver in Infancy and Childhood, Am. J. M. Sc. **156**:79, 1918. Boyce, F. F., and McFetridge, E. M.: Primary Carcinoma of the Liver, with Report of Twenty-Eight Additional Cases, Internat. S. Digest **18**:67, 1934. Martinez, J. A.: Primary Carcinoma of the Liver: Description of an Unusual Case, Lancet **2**:1293, 1935. Smith, K. J.: Primary Carcinoma of the Liver, J. Lab. & Clin. Med. **18**:915, 1932. Brines, O. A.: Primary Tumors of Liver, Am. J. Clin. Path. **3**:221, 1933. Tull, J. C.: Primary Carcinoma of the Liver: A Study of One Hundred and Thirty-Four Cases, J. Path. & Bact. **35**:557, 1932. Strong and Pitts,[10c] Counseller and McIndoe,[10d] Von Glahn and Lamb.[10b] Williamson, C. S.: Primary Carcinoma of the Liver, M. Clin. North America **8**:453, 1924. Friedenwald, J., and Fried, H.: Primary Cancer of the Liver, Am. J. M. Sc. **168**:875, 1924. Fried, B. M.: Primary Carcinoma of the Liver, ibid. **168**:241, 1924. Karsner, H. T.: A Clinico-pathological Study of Primary Carcinoma of the Liver, Arch. Int. Med. **8**:238 (Aug.) 1911. Milne, L. S.: Primary Epithelial Tumor Growth in the Liver, J. Path. & Bact. **13**:348, 1909.

10. (*a*) Culpepper, A. L., and von Haam, E.: Primary Carcinoma of the Liver with Extensive Metastasis to the Right Heart, and Tumor Thrombosis of the Inferior Vena Cava, Am. J. Cancer **21**:355, 1934. (*b*) Von Glahn, W. C., and Lamb, A. R.: Primary Carcinoma of the Liver, M. Clin. North America **8**:29, 1924. (*c*) Strong, G. F., and Pitts, H. H.: Primary Carcinoma of the Liver, Arch. Int. Med. **46**:105 (July) 1930. (*d*) Counseller, V. S., and McIndoe, A. H.: Primary Carcinoma of the Liver, ibid. **37**:363 (March) 1926. (*e*) Fabyan, M.: A Case of Primary Carcinoma of the Liver Supervening in a Cirrhotic Liver, Bull. Johns Hopkins Hosp. **18**:351, 1907.

to swell. The swelling was marked for several days. It always diminished and sometimes disappeared during the night. Shortly afterward the right foot began to swell. The patient continued his work until the day before admission, at which time edema of both extremities was very marked and extended about half way between the knee and the hip. Three weeks previous to admission and two weeks after the onset of edema, the pain in the back was noticed. It was in the right lumbar region and was constant and aching in character, but sometimes so severe as to permit no rest or sleep. It did not radiate and was not increased by postural changes. It was relieved, however, by sitting up. This symptom caused the patient to seek admission to the hospital. He had not been aware of fever. He urinated about ten times daily, with equal distribution between night and day. He had had gonorrhea and a penile sore twelve years before admission. The family, social and marital histories were irrelevant. He persistently denied that he had noticed any dyspnea. It may be emphasized that he had been doing hard farm work until the day before admission. He had walked five miles and worked until midnight twice a week in addition to his farm duties.

Physical Examination.—The patient was well developed and well nourished. He did not appear acutely ill. There were no important abnormalities in the head, neck, lungs or heart. The blood pressure was 160 systolic and 98 diastolic. The liver was easily palpated about 4 cm. below the right costal margin in the midclavicular line, at about which point a distinct notch or nodule was felt. The liver was firm; the edge was not sharp, and there was no tenderness. The abdomen was otherwise normal. The patient was not jaundiced. The rectum and the genitalia were normal. There was questionable tenderness of uncertain significance in the right costovertebral angle. There was marked pitting edema with shiny skin up to about 6 inches (15 cm.) above the knees. The temperature was normal on admission.

Laboratory Data.—The urine contained a trace of albumin on three occasions. Results of microscopic examination were always normal. Examination of the blood showed the value for hemoglobin to be 90 per cent; the white cell count was 6,750 per cubic millimeter, with 17 per cent lymphocytes and 83 per cent polymorphonuclears. No malarial organisms or filarias were seen. The Wassermann reaction of the blood was strongly positive on two occasions. The urea nitrogen content of the blood was 35 mg. and the creatinine content 2.9 mg. per hundred cubic centimeters on the day before death. Roentgenograms of the chest showed no pathologic condition of the lungs, mediastinum or great vessels. A large liver shadow and elevation of the right dome of the diaphragm were seen. Anteroposterior and lateral roentgenograms of the spine showed no evidence of disease.

Course in Hospital.—The patient was given complete rest in bed and was able to lie flat on his back or abdomen without dyspnea. After he had spent a week in bed the edema was much less, but never disappeared. His only complaint was backache. Although there was some general improvement, it was very slight. There were elevations of temperature to 99 F. and on several occasions to 100 or 101 F., but this was not continuous.

The patient was not aware of any significant loss of weight. Because of the history of a penile lesion, the positive Wassermann reaction and the hard, irregular liver, a diagnosis of gummas or syphilitic cirrhosis of the liver was considered, and he was given potassium iodide and bismuth medication. We were unable, however, to account for the marked dependent edema on this basis. Filariasis was considered, but no filarias were seen in either of two examinations of the blood,

one of which was made at night. Because of the possibility of a malignant retroperitoneal tumor compressing or invading the inferior vena cava, roentgenograms of the kidneys, ureters and bladder were made, but no abnormality of this sort was suggested by the findings. The patient was then transferred to the urologic service for retrograde pyelographic studies. While a slight urethral stricture was being progressively dilated as a preliminary procedure, his condition became much worse, and he was transferred back to the medical service.

Examination at this time, one month after admission, showed him to be orthopneic. The veins of the neck were engorged, and there was a marked increase in the size of the liver, which extended to the umbilicus and was very tender. There were moderate ascites and extreme edema of the lower part of the trunk, the scrotum, the penis and the lower extremities. In addition, slightly dilated veins were noted for the first time on the upper part of the abdomen and the lower aspect of the thorax on both sides. Pressure on the upper part of the abdomen, particularly over the liver, produced marked increase in the jugular engorgement. The patient complained of extreme backache, which required codeine or morphine for relief. From this point the course was rapidly downhill. Death occurred on October 25, forty-eight days after admission. Autopsy was performed by Dr. J. R. Schenken, of the department of pathology, thirty-six hours after death.

The anatomic diagnosis was primary carcinoma of the liver (of liver cell type) with widespread hepatic involvement (weight of liver, 4,000 Gm.) and extensive tumor invasion of branches of the hepatic veins; tumor (carcinomatous) thrombus of the inferior vena cava and right auricle (filled) and tumor embolism of the pulmonary arteries; cirrhosis of the liver; bilateral edema of the lower extremities, and ascites, with serosanguineous fluid.

In spite of the numerous findings which suggested congestive heart failure at the end, the clinical course was definitely against such a diagnosis. The marked edema of the legs on admission with no shortness of breath or jugular distention deserved further emphasis in this connection. The pulse rate was about 84 much of the time, even during the last few days. The dilatation, though slight, of the veins of the upper part of the abdomen and the lower part of the thorax pointed to obstruction of the inferior vena cava as the cause of edema of the lower portion of the body. This, however, did not explain the orthopnea or the jugular distention. Nor would it account for the increase in size or the tenderness of the liver unless the obstruction was at or above the diaphragm.

The extreme backache of which the patient complained and because of which he sought admission to the hospital was not explained clinically. Metastatic spinal disease was ruled out by roentgenograms. The possibility of an abdominal aneurysm with spinal erosion was ruled out in the same manner. The fact that the pain was relieved, at least in the beginning and to a certain extent at the end, by the patient's assuming a sitting or standing position leads one to suggest as a possible explanation that the pain was due to the pressure of the large and heavy liver against the spine.

Pleasants [11] called attention to lumbar pain as a feature of thrombosis of the vena cava of inflammatory and tumor origin, but he did not explain the mechanism of the pain.

The possibility of the pain being due to increased pressure in the renal veins, with renal congestion, is perhaps worth consideration.

The final clinical diagnosis rested between tumor thrombosis (primary origin unknown) of the inferior vena cava and syphilitic cardiovoscular disease with congestive heart failure.

COMMENT

I have found in the literature 11 instances of tumor thrombosis of the inferior vena cava or the right auricle or both which resulted from primary carcinoma of the liver. To this list I am adding a case.

I have arranged my analysis of the complaints, physical findings and laboratory data (including autopsy observations) in tables 1, 2 and 3, respectively. No clinical data are available on the cases reported by Rowen and Mallory [1] and by Reynaud.[12]

Seven of the cases (6 to 12, inclusive, in the tables) have been previously reviewed by Simpson.[8] My new case is included in the tables as case 5.

The difficulty with which primary carcinoma of the liver with tumor thrombosis of the inferior vena cava is diagnosed is evidenced in table 1. In no instance was the diagnosis made correctly. The fact that a clinical diagnosis was not given in 9 of the 12 cases is ground for the belief that the clinical diagnosis was wrong. In my case (case 5) the possibility of tumor thrombosis of the inferior vena cava was suspected, and as it is well recognized that malignant tumors of the kidney are the principal source of such thrombosis, the patient was prepared for a urologic examination, when he suddenly became much worse and died shortly thereafter.

The suspicion of obstruction of the inferior vena cava was later more tangibly supported by the development of dilatation of the superficial veins of the anterolateral portions of the thorax and abdomen. Simpson [8] has called attention to the infrequent occurrence of this classic diagnostic criterion of thrombosis of the inferior vena cava. Dilatation of the superficial veins was not present in any of the 4 cases in his own series and was present in less than one half the cases he reviewed. Of the 4 cases of primary carcinoma of the liver reviewed by me (in

11. Pleasants, J. H.: Obstruction of the Inferior Vena Cava, with a Report of Eighteen Cases, Johns Hopkins Hosp. Rep. **16**:343, 1911.

12. Reynaud, P.: Cancer du rein droit: Presence de la matière cancereuse dans la veine rénale, dans la veine cave et dans la bassinet, Bull. Soc. anat. de Paris **8**: 60, 1833; cited by Simpson.[8]

TABLE 1.—*Clinical Data in Twelve Cases of Tumor Thrombosis of Inferior Vena Cava and/or Right Auricle*

TABLE 1.—*Clinical Data in Twelve Cases of Tumor Thrombosis of Inferior Vena Cava and/or Right Auricle*

Case	Age	Sex	Race	First Symptoms	Jaundice	Other Complaints					Clinical Diagnosis	Stay in Hospital	Length of Illness Prior to Hospitalization	Author
						Abdominal Swelling	Edema of Lower Extremities	Pain	Shortness of Breath	Weakness				
1	56	M	Negro	Swelling of the ankles (progressive)	Slight at autopsy	Present	Present (entire lower limbs and abdominal wall)	Dull pain in region of stomach	Marked for 3 weeks prior to admission	Not mentioned	Arteriosclerotic heart disease with decompensation	35 days (death)	5 weeks	Culpepper and von Haam
2	73	M	White	Swelling of legs at night	Present (late)	Present	Present	Constant dull epigastric pain	Present	Present and progressive	Diabetes (20 years); otherwise not mentioned	18 days (death)	6 weeks	Von Glahn and Lamb
3	54	M	White	Swelling and discomfort in abdomen	Slight, but increased before death	Present	Present from beginning	.....	Dyspnea on exertion	Present	Not mentioned	11 days (death)	7 weeks	Von Glahn and Lamb
4	62	M	Negro	Long illness with weakness and swelling of abdomen	Not mentioned	Present	Not mentioned	Not mentioned	Not mentioned	Present 9 months	Not given	.....	9 months	Fabyan
5	35	M	Negro	Swelling of ankles	None	Developed in hospital	Present (thighs and abdominal wall)	Lumbar region of back; severe	None on admission; orthopnea began in hospital	None on admission	Tumor thrombus of inferior vena cava vs. syphilitic aortitis with congestive heart failure	49 days	5 weeks	Gregory (present case)
6	51	M	White	Swelling of lower extremities	None	Present	Present	.....	.....	Present	Not mentioned	.....	.....	Chalier and Garin
7	25	M	White	Cough; swelling of legs	None	Present	Present	.....	.....	Present	Not mentioned	5 months	.....	Gull
8	49	M	White	Progressive edema of legs	Present	Present	Present	.....	.....	.....	Not mentioned	2 weeks	.....	Lanceraux
9	51	F	White	Weakness; dyspnea; swelling of legs	None	Present	Marked (thighs)	.....	Present	Present	Not mentioned	2 months	.....	Michelland
10	Clinical data not available							.....	.....	.....	Not given	.....	.....	Reynaud
11	70	F	White	Swelling of lower extremities	None	.....	Present	.....	.....	.....	Not given	2 weeks	.....	Sternberg
12	43	M	White	Chills; swelling of lower extremities	None	Present	Present (also abdominal wall and scrotum)	.....	.....	.....	Not given	2 months	.....	Vimont

TABLE 2.—*Physical Findings in Twelve Cases of Tumor Thrombosis of Inferior Vena Cava and/or Right Auricle*

Case	Liver	Ascites	Cardiac Signs	Edema of Lower Extremities	Edema of Upper Extremities	Collateral Circulation	Veins of Neck	Cyanosis	Temperature, Degrees F.	Spleen
1	Not palpated, owing to abdominal distention, but enlarged on percussion	Present	Slightly enlarged (?) dyspnea; engorged veins of neck	Massive	Not mentioned	None mentioned	Distended; pulsating	Lips and Nose	98.4	Enlarged on percussion
2	Halfway to umbilicus; hard and firm	Present	Enlarged (?)	Present	Not mentioned	None mentioned	Not mentioned	Not mentioned	98.6	Just felt
3	Two inches below right costal margin	Present	None recorded	Present	Not mentioned	Few dilated veins over lower part of thorax	Not mentioned	Not mentioned	Afebrile	Not felt
4	Five inches below right costal margin; nodular	Not mentioned	Not mentioned	Present (autopsy)	Not mentioned	One prominent superficial abdominal vein	Not mentioned	Not mentioned	Not given	Not mentioned
5	To umbilicus	Present	Orthopnea; jugular engorgement	Massive	None	Present on both sides of upper part of abdomen and lower part of thorax	Engorged	Not observed	Occasionally 100-101	Not felt
6	.....	Present	None	Present	.....	None				
7	.....	Present	None	Present	.....	Present				
8	.....	Present	None	Present	.....	None				
9	.....	Present	.....	Present	.....	None				
10	Clinical data not available									
11	.....	None	None	Present	.....	None				
12	.....	Present	None	Present	.....	Present; superficial				

TABLE 3.—*Laboratory Findings in Twelve Cases of Tumor Thrombosis of Inferior Vena Cava and/or Right Auricle*

										Deep	Other	Histologic

TABLE 3.—*Laboratory Findings in Twelve Cases of Tumor Thrombosis of Inferior Vena Cava and/or Right Auricle*

Case	Urine	Blood*	Ascitic Fluid	Thrombosis of Vena Cava	Invasion of Hepatic Veins	Invasion of Portal Branches	Retrograde Thrombus	Thrombus in Right Auricle	Pulmonary Tumor Emboli	Other Metastases	Deep Collateral Circulation	Other Pathologic Conditions	Histologic Type of Primary Tumor	Heart	Liver, Gm.	Spleen
1	Albumin; granular casts	Hb. 60%; R.B.C. 3,890,000; W.B.C. 15,200; Wass. (—)	1,500 cc.; dark brown	Present; occluded	Present	Present	Blood clot extending to common iliac veins	Tumor thrombus (large)	Few	Retroperitoneal and hepatic ligament	No increase mentioned	Portal cirrhosis; pericardial effusion	Hepatoma	300 Gm.; valves normal	2,900	400 Gm.
2	Hyaline casts	R.B.C. 4,900,000; W.B.C. 9,600; Wass. (—)	2,400 cc.; turbid	Present; occluded	Present	Present; portal thrombosis	None	None	Present	None	No increase mentioned	Cirrhosis; hemosiderosis	Diagnosis not made; hepatoma likely	Weight not given	1,670	Not mentioned
3	Few hyaline casts	Hb. 105%; R.B.C. 5,000,000; W.B.C. 15,200; Wass. (—)	Character and amount not mentioned	Present; occluded	Present	Present	None	None	None	None	Increased in hepatic ligaments and peritoneal surface of diaphragm	Cirrhosis of liver; pneumonia	Hepatoma	Condition not mentioned	1,300	Moderately enlarged
4	Data not given	Data not given	3 liters; straw colored	Complete occlusion	Present	Present	None	None	Present	Lungs	Not mentioned	Liver cirrhosis; esophageal varices	Not mentioned	Coronary sclerosis	1,300	Not enlarged
5	Trace of albumin; microscopic examination normal	Hb. 90%; W.B.C. 6,750; L. 17%; P. 83%; no malaria organisms; no filarias; Wass. 4 plus	800 cc. serosanguineous fluid	Present	Present to marked degree	Present	Not mentioned	Present, almost filling right auricle	Present	None	Not mentioned	Cirrhosis of liver	Hepatoma	450 Gm.	4,000	250 Gm.
6	Albumin	.....	Present	Present	Present	.....	Present; entire inferior vena cava	Large distending right auricle	.....	.....	.....	.....	Not differentiated			
7	.....	.....	Present	Present	Present	.....	Extended to renal veins	.....	.....	.....	Azygos and intercostal veins	.....	Not differentiated			
8	.....	.....	Present	Present	Present	Present	.....	.....	.....	.....	.....	.....	Hepatoma			
9	Albumin	.....	Present	Present	Present	.....	Extended to common iliac veins	Present								
10	.....	.....	.....	Present	Present	.....	.....	.....	.....	.....	.....	.....	Not given			
11	.....	.....	None	Present	Present	.....	.....	Present	.....	.....	None	.....	Not given			
12	No albumin	.....	Present	Present	Present	.....	Tumor thrombus to renal veins; blood thrombus to femoral veins	None	.....	.....	.....	.....	Not differentiated			

* In the table "Hb." indicates hemoglobin content; "R.B.C.," red blood cells; "W.B.C.," white blood cells; "Wass.," the Wassermann reaction; "L.,"lymphocytes, and "P.," polymorphonuclears.

addition to Simpson's cases), this sign was noted to a slight degree in 2. In 5 of the 11 cases on which I have clinical data dilated superficial veins of the abdomen or thorax were observed. This appears to indicate that the incidence of superficial venectasis is approximately the same in thrombosis of the vena cava from carcinoma of the liver as in tumor thrombosis of the inferior vena cava from other sources.

Most writers have called attention to the rapidly fatal course of primary carcinoma of the liver. The cases reviewed by me confirm their observations. With the exception of case 4 (reported by Fabyan), in which the patient had probably had hepatic cirrhosis for most of the nine months of his sickness, the average duration of symptoms prior to admission to the hospital was five to six weeks, and the average stay in the hospital before death was twenty-eight days in the 4 cases on which I have sufficient data.

My primary interest in the study of this subject is in defining the criterion for the diagnosis of primary carcinoma of the liver with tumor thrombosis of the inferior vena cava, the right auricle or both. I have found no instance in which tumor thrombosis of the right auricle resulted from primary carcinoma of the liver in the absence of thrombosis of the inferior vena cava unless such thrombosis took place by extension through the diaphragm and the wall of the auricle.[10c]

Although small pulmonary emboli of tumor cells were commonly observed, I found no instance in which these emboli caused sudden death, as Judd and Scholl [13] reported in cases of malignant renal tumors, particularly at or immediately after operative procedures.

The two uniformly occurring complaints were swelling of the lower extremities (usually progressive) and swelling of the abdomen. Likewise, edema of the lower extremities and ascites were the only signs uniformly present.

I believe it to be significant that dependent edema was among the first symptoms noted in all but 1 case (case 4). As I have observed, it seems likely that the primary complaints of the patient in this case were due to cirrhosis of the liver with portal decompensation and that the signs of primary carcinoma of the liver were superimposed as late manifestations. The initial dependent edema is probably not to be explained on the basis of tumor thrombosis of the inferior vena cava alone.[14] The development of this edema in the absence of any short-

13. Judd, E. S., and Scholl, A. J.: Thrombosis and Embolism Resulting from Renal Tumors, J. A. M. A. **82**:75 (Jan. 12) 1924.

14. (*a*) Winternitz, M. C.: Primary Carcinoma of the Liver, Johns Hopkins Hosp. Rep. **17**:143, 1916. (*b*) Bejan, J., and Cohn, M.: Sur la ligature de la veine cave inférieure; étude expérimentale, Rev. de chir. **43**:302, 1911. (*c*) Cole, H. P.: Laceration of the Inferior Vena Cava Repaired by Suture; Recovery, Ann. Surg. **66**:43, 1917. Footnotes 8 and 10 *e*.

ness of breath is an argument against a diagnosis of heart disease. It is essential, therefore, when patients with such edema are seen late and have some shortness of breath that a complete history of the sequence of events be obtained.

This point is well illustrated by cases 1, 2 and 5, particularly cases 1 and 5, in which there was marked edema of the lower extremities for two and four weeks, respectively, before the onset of any respiratory difficulty. Culpepper and von Haam [10a] concluded that thrombosis of the right auricle occurred before thrombosis of the vena cava in their case. From an analysis of their clinical data, I believe that thrombosis of the vena cava occurred before the right auricle.

Dyspnea of marked degree was present in only 3 patients (1, 5 and 8). Some dyspnea on exertion was present in patients 2 and 3. In patients 1, 5 and 8, who had severe dyspnea (orthopnea), thrombosis of the right auricle was observed. This was observed also in case 6; no statement, however, was made regarding dyspnea. The correlation between extreme dyspnea and auricular thrombosis, although not complete, is high. From this and theoretic considerations, I believe that it is probably an important point. Therefore, if malignant thrombosis of the inferior vena cava is probable, the sudden onset, after weeks of dependent edema, of severe dyspnea or orthopnea, marked increase in the size of the liver, ascites and jugular engorgement is strong evidence to support the clinical diagnosis of thrombosis of the right auricle.

Jaundice was present in 4 of the 11 cases in which there were clinical data: to a slight degree in 3 cases [15] and to a moderate degree before death in 1 case. In the latter, the jaundice was associated with the presence of bile in the urine. Smith [16] has reported a much greater incidence of jaundice, observing it in practically all of 23 cases of primary carcinoma in which the diagnosis was proved at autopsy.

Reference to table 1 will show that pain is an inconspicuous part of the general picture of carcinoma of the liver with obstruction of the vena cava. As I have pointed out, pain in the lumbar region of the back was severe in my case (case 5) and was the immediate cause of the patient's seeking medical attention.

Judging from the data in cases 1 to 5, moderate to marked enlargement of the liver is present in primary carcinoma with obstruction of the vena cava. As I have pointed out, given a large liver and dependent edema as the only complaints or signs, the sudden marked increase of edema, with appearance of ascites and shortness of breath, should suggest thrombosis of the right auricle superimposed on thrombosis of the inferior vena cava.

15. Rowen and Mallory.[1] Orth.[2] Culpepper and von Haam.[10a]

16. Smith, K. J.: Primary Carcinoma of the Liver, J. Lab. & Clin. Med. **18**:915. 1933.

Von Glahn and Lamb [10b] expressed the opinion that when the diagnosis rests between cirrhosis with portal decompensation and primary carcinoma of the liver, the presence of a large liver with ascites is in favor of the latter. They made the point that hepatic cirrhosis is seldom associated with ascites when the liver is still large.

The laboratory data (table 3) appear to offer no information of differential diagnostic value. The urine in 4 of our cases showed albumin. Simpson [8] called attention to the infrequency of abnormal urinary findings even in the presence of complete thrombosis of the vena cava above the renal veins. He explained this as being due to the ease with which the renal capsular collateral veins reestablish adequate venous circulation. In my case the urea nitrogen content of the blood was 35 mg. and the creatinine content 2.9 mg. per hundred cubic centimeters. The kidneys weighed 260 and 300 Gm. and showed marked congestion, which was probably the cause of the slight nitrogen retention.

In view of the fact that malignant tumors of the adrenal glands, kidneys, testicles and liver with tumor thrombosis of the inferior vena cava and/or right auricle may present the end picture of edema, ascites, shortness of breath and enlargement of the liver, is there any means by which one may differentiate primary carcinoma of the liver with thrombosis of the vena cava from these other conditions? I believe that this is possible. Although Simpson [8] has shown that of the four common causes of tumor thrombosis of the inferior vena cava carcinoma of the liver ranks third (it formed only 10 per cent of his series), it seems likely that careful attention to the details of development of symptoms may make it possible to differentiate primary carcinoma of the liver with tumor thrombosis of the vena cava from the other conditions causing tumor thrombosis of the vena cava. It is unlikely that tumors of the testicles producing thrombosis of the vena cava will present any problem, because of the ease with which these organs may be examined.

Table 1 reveals that except in case 4, in which the patient had been ill for months, probably as a result of the cirrhosis, swelling of the lower extremities was invariably the first or among the first symptoms noted. In Simpson's review,[8] edema of the lower extremities was noted as the initial symptom in only 5 of 32 cases of thrombosis of the vena cava from renal malignant tumor, in none of 13 cases of malignant tumors of the testis with thrombosis of the vena cava and in none of the cases of malignant tumors of the adrenal glands or pancreas producing obstruction of the vena cava. On the other hand, edema of the lower extremities was the first symptom in all 6 cases of carcinoma of the liver on which clinical data were recorded by Simpson.

Numerous authors, including Simpson[8] Winternitz,[14a] Fabyan[16e] Bejan and Cohn,[14b] Cole[14c] and Judd and Scholl,[13] have called attention to the mildness or absence of circulatory disturbance in the lower extremities with marked obstruction of the vena cava. Judd and Scholl reported 3 cases of malignant tumors of the kidney filling the entire inferior vena cava, with no edema. Likewise, Woodruff and Levine[17] reported a case of hypernephroid carcinoma of the kidney with tumor thrombosis of the entire vena cava and of the right auricle in which the disease ran its entire course without any edema of the lower extremities. There was, however, 1,500 cc. of fluid in the abdomen at postmortem examination.

In none of the reported cases of primary carcinoma of the liver with thrombosis of the vena cava has the patient failed to show edema of the lower extremities. As has been noted, this was almost uniformly the first symptom or sign which developed. I believe the explanation for this phenomenon lies in the disturbance of one of the main collateral systems when thrombosis of the vena cava results from primary carcinoma of the liver.

Simpson,[8] among others, has pointed out that renal function does not suffer as a result of occlusion of the vena cava above the renal veins. Although it is difficult to prove, it seems likely that edema and ascites, particularly the latter, do not develop until the thrombus reaches the level of the hepatic veins.

If this is true, it is easy to understand why edema of the lower limbs is so constantly observed as the first manifestation of thrombosis of the vena cava from primary carcinoma of the liver. The circulation may be obstructed by thrombosis of the hepatic veins, which is widespread in carcinoma of the liver, and the patient may not show edema early, as is usually the case in cirrhosis with portal obstruction. Likewise, as has been pointed out, the inferior vena cava anywhere below the hepatic veins may be thrombosed without producing edema. It appears likely that the portal system offers one of the means of collateral return. If, however, the hepatic veins are already occluded, or partly so, by tumor thrombosis, the thrombosis of the vena cava developing from this would more easily produce edema as a result of the portal system's failure to act as a collateral.

SUMMARY

The literature on primary carcinoma of the liver with respect to tumor thrombosis of the inferior vena cava and the right auricle is reviewed. The 7 cases previously reported by Simpson, 4 additional

17. Woodruff, L. W., and Levine, V.: Hypernephroid Carcinoma of the Kidney, J. A. M. A. **106**:1544 (May 2) 1936.

cases found in the literature and a case of my own, reported here, have been studied particularly from the standpoint of the differentiation of primary carcinoma of the liver with thrombosis of the inferior vena cava and right auricle from tumor thrombosis of the inferior vena cava associated with malignant neoplasms of the kidneys, adrenal glands, testicles or pancreas.

CONCLUSIONS

Tumor thrombosis of the inferior vena cava and/or right auricle is a rare complication of primary carcinoma of the liver. It occurred in 5, or 2.1 per cent, of 234 cases.

Dilatation of the superficial veins of the abdomen or thorax occurred in approximately 50 per cent of cases of primary carcinoma of the liver with tumor thrombosis of the inferior vena cava.

The extreme pain in the lumbar portion of the back which was observed in my patient and was also noted by Pleasants [11] may possibly be explained by the marked passive congestion of the kidneys (weight, 260 and 300 Gm.).

Edema of the lower extremities was the first or among the first symptoms or signs noted in 11 of 12 cases of thrombosis of the vena cava from primary carcinoma of the liver which I studied. In Simpson's it occurred as an initial symptom in only 5 of 32 cases of renal malignant tumor, in none of 13 cases of malignant tumor of the testis and in none of the cases of malignant tumors of the adrenal glands or pancreas associated with tumor thrombosis of the inferior vena cava.

Marked invasion of the hepatic veins with tumor thrombus interferes with, if it does not actually prevent action of, the portal circulation as an important collateral return from the lower part of the body when the inferior vena cava becomes occluded with tumor. This is offered as an explanation for the almost uniform occurrence of edema of the lower extremities as an initial symptom of primary carcinoma of the liver with tumor thrombosis of the inferior vena cava. This is in contrast to the extremely low incidence of edema of the extremities as an initial symptom of other malignant growths associated with tumor thrombosis of the inferior vena cava.

Edema of the lower extremities as an initial symptom not associated with shortness of breath or increased venous pressure but associated with a large liver is suggestive evidence of primary carcinoma of the liver with tumor thrombosis of the inferior vena cava.

The occurrence of orthopnea, marked increase in the venous pressure, sudden increase in edema of the extremities and the scrotum and sudden increase in the size and tenderness of the liver in a patient who presents reasonable evidence of tumor thrombosis of the inferior vena cava should be interpreted as good evidence that a tumor thrombus has formed in the right auricle.

THIOCYANATE DERMATITIS

REPORT OF A CASE

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The ability of the thiocyanates to lower the blood pressure was observed as early as 1903 by Pauli,[1] but the drugs were not introduced in the treatment of hypertension until 1924, by Westphal.[2] Their use has been limited, however, because of the toxic effects frequently produced. In 1932 Goldring and Chasis[3] reported the toxic symptoms which occurred in 13 of 50 patients treated for hypertension with thiocyanate. These symptoms consisted of muscular fatigue, nausea and vomiting, mental confusion, hallucinations and motor aphasia. They also reported 2 deaths, preceded by delirium, convulsive twitchings and coma. They pointed out that some persons show a distinct susceptibility to the drug.

In 1926 Takacs[4] reported the first case of dermatitis due to thiocyanate. This was a papular eruption which occurred after the ingestion of 1 Gm. of potassium thiocyanate daily for nine days. Since that time there have been reported numerous cases of mild maculopapular cutaneous eruptions due to the thiocyanates. Gager[5] reported 2 cases,

Studies and contributions from the Department of Internal Medicine, service of Dr. Cyrus C. Sturgis, and the Department of Dermatology and Syphilology, service of Dr. Udo J. Wile, University of Michigan Medical School.

1. Pauli, W.: Ueber Ionenwirkungen und ihre therapeutische Verwendung, München. med. Wchnschr. **50**:153-157 (Jan. 27) 1903.

2. Westphal, K.: Untersuchungen zur Frage der Entstehungsbedingungen des genuinen arteriellen Hochdruckes: I. Die paradoxe Gefässreaktion auf Abschnürung bei arterielle Hochdruck, Ztschr. f. klin. Med. **101**:545-557, 1925.

3. Goldring, W., and Chasis, H.: Thiocyanate Therapy in Hypertension: I. Observations on Its Toxic Effects, Arch. Int. Med. **49**:321-329 (Feb.) 1932.

4. Takacs, L.: Versuche mit Rhodansalzen: I. Einfluss des Rhodan auf Magensekretion, weisse Blutkörperchen, Pulsschlag und Blutdruck, Ztschr. f. d. ges. exper. Med. **50**:432-439, 1926.

5. Gager, L. T.: The Incidence and Management of Hypertension, with a Note on Sulfocyanate Therapy, J. A. M. A. **90**:82-86 (Jan. 14) 1928.

Goldring and Chasis [8] noted a case and Borg [6] also mentioned 1. In 1937 Baker and Brunsting [7] stated that they had observed several cases of these mild cutaneous reactions. Barker [8] stated that in ten years' experience with this group of drugs, he had observed no severe cutaneous reactions but had noted several cases of mild dermatitis.

Thiocyanates have been used at the University of Michigan Hospital for about three years in selected cases of essential hypertension. During this time a mild, nondescript, erythematous dermatitis has been observed in 4 or 5 patients receiving the drug. These patients have not presented other toxic symptoms, and the eruptions have promptly subsided on discontinuance of the drug.

Regarding the more severe cutaneous reactions, reports of only 5 cases are found in the literature. Logefeil [9] reported 2 cases, in which a dry, scaly, pruritic dermatitis developed on the entire body, associated with fever and moderate prostration. In 1929 Weis and Ruedemann [10] described a generalized erythematous dermatitis which appeared on the tenth day of administration, 2.7 Gm. having been ingested. The eruption reached its height in four days and became exfoliative. Later, small doses of thiocyanate were again given, and a similar eruption developed. Ayman [11] observed a case of generalized maculopapular dermatitis which developed on the eighth day of medication, after 4.8 Gm. of potassium thiocyanate had been taken. The eruption was associated with weakness, abdominal cramps and a temperature of 99.5 F. In 1937 Baker and Brunsting [7] reported a case of severe dermatitis. This acute generalized papulourticarial eruption was associated with conjunctivitis, pharyngitis, elevation of the temperature and lowering of the blood pressure. No concomitant blood cyanate determinations were reported in any of these cases.

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6. Borg, J. F.: Experiences in the Use of the Sulfocyanates, Minnesota Med. **13**:293-296 (May) 1930.

7. Baker, T. W., and Brunsting, L. A.: Dermatitis Medicamentosa Resulting from the Administration of Sulfocyanates in the Treatment of Hypertension, J. A. M. A. **108**:549-550 (Feb. 13) 1937.

8. Barker, M. H.: Personal communication to the authors.

9. Logefeil, R. C.: Observations on the Use of Potassium Sulfocyanate (Rhodan) in the Treatment of Essential Hypertension, Minnesota Med. **12**:151-159 (March) 1929.

10. Weis, C. R., and Ruedemann, R.: Exfoliative Dermatitis from Potassium Sulphocyanate Therapy, J. A. M. A. **93**:988 (Sept. 28) 1929.

11. Ayman, D.: Exfoliative Dermatitis from Potassium Thiocyanate, J. A. M. A. **93**:1671 (Nov. 23) 1929.

Recently Barker [12] developed a practical method of performing blood thiocyanate determinations by modifying Schreiber's [13] technic. He observed that the optimum therapeutic level is 8 to 12 mg. per hundred cubic centimeters of blood and that significant toxicity begins to appear at levels of 15 to 30 mg. He noticed that the amount of drug necessary to produce a given level in the blood varies widely in different individuals but that if the blood concentration is studied the dosage can usually be regulated so as to reduce the blood pressure without producing toxic symptoms.

The case which we wish to present is of special interest because, first, the dermatitis was of the unusual severe urticarial type associated with marked constitutional symptoms; second, the eruption developed while the patient was in the hospital, so that daily observations and study were possible throughout the course of the reaction, and, third, blood thiocyanate determinations were obtained.

REPORT OF CASE

C. W., a physician aged 41, entered the hospital on July 18, 1938. He was known to have had hypertension for five years, and since January 1937 his blood pressure had averaged 200 to 210 systolic and 120 to 130 diastolic. In May 1938 he noticed blurring of vision in the right eye. He gave a history of urticaria in childhood, attacks of migraine in early adult life and also symptoms of peptic ulcer, which were controlled by a dietary regimen. He stated that both he and his father were "sensitive" to acetylsalicylic acid.

Physical examination revealed a well developed, moderately overweight, middle-aged man. Ophthalmoscopic examination showed slight edema of both disks and many small discrete areas of exudation. The right fundus presented evidence of inactive central chorioretinitis. The retinal vessels were spastic but not sclerotic. Examination of the heart showed the apex beat to be 12.5 cm. to the left of the midsternal line in the fourth intercostal space. The heart sounds were of good quality. An occasional extrasystole was present, and the aortic second sound was accentuated. A gallop rhythm was noted at the apex. The blood pressure was 230 systolic and 160 diastolic. The pulmonary fields were clear. The edge of the liver was just palpable on deep inspiration. There was no edema. The pupillary and tendon reflexes were physiologic.

Electrocardiographic study showed definite left axis deviation, with an inverted T wave in all leads, together with notching and slurring of the QRS complex. The heart was of borderline size by orthodiagraphic and teleroentgenographic measurements.

Urinalysis showed a one plus reaction for albumin and one or two finely granular casts per low power field. A urea clearance test showed 80 per cent of normal clearance for the first hour specimen and 71 per cent for the second

12. Barker, M. H.: The Blood Cyanates in the Treatment of Hypertension, J. A. M. A. **106**:762-767 (March 7) 1936.

13. Schreiber, H.: Ueber den Rhodangehalt in menschlichen Blutserum, Biochem. Ztschr. **163**:241-251, 1925.

hour. The urine was concentrated to a specific gravity of 1.021, according to the Newburgh-Lashmet concentration test.[14]

The nonprotein nitrogen content of the blood was 33.5 mg. per hundred cubic centimeters. The Kahn test of the blood gave a negative reaction. The hemoglobin value was 95 per cent (Sahli), and the red blood cell count was 5,200,000 per cubic millimeter. The total white blood cell count was 6,650 per cubic millimeter, with a differential count showing 71 per cent neutrophils, 3 per cent eosinophils, 13 per cent lymphocytes and 5 per cent monocytes.

The diagnosis was essential hypertension and hypertensive heart disease, with hypertensive neuroretinitis and right inactive chorioretinitis.

A period of medical management was advised. The patient was placed at rest in bed and given 0.032 Gm. of phenobarbital four times daily. On July 22

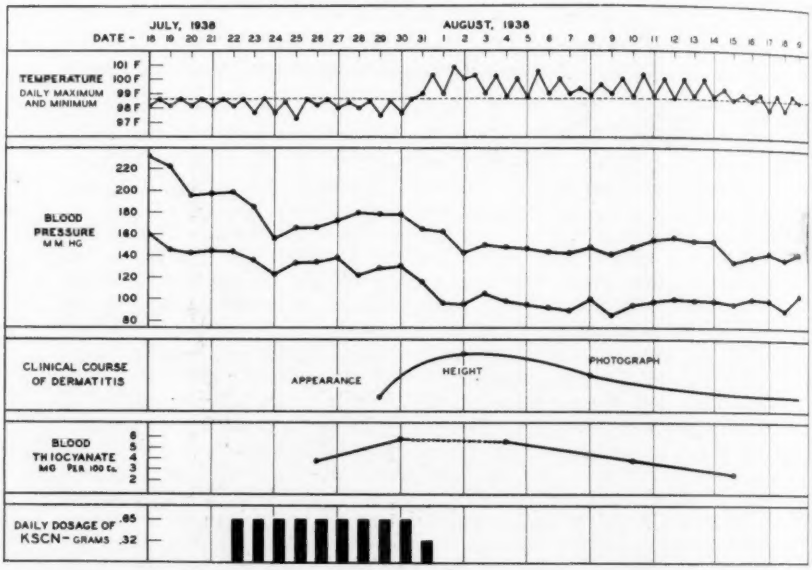

Fig. 1.—Correlation of the clinical course of the reaction with the concentration of thiocyanate in the blood.

thiocyanate therapy was instituted. This consisted of 0.32 Gm. of potassium thiocyanate given in a peppermint water vehicle twice daily. The blood pressure had been 196 systolic and 144 diastolic for four days when the thiocyanate treatment was started. On July 26 the blood pressure was 160 systolic and 130 diastolic. The patient had then received only 2.6 Gm. of potassium thiocyanate, and the cyanate concentration of the blood was 3.7 mg. per hundred cubic centimeters.

On the morning of July 29, the eighth day of thiocyanate therapy, after 4.55 Gm. of the drug had been ingested, a pruritic eruption of the skin appeared. It was

14. Lashmet, F. H., and Newburgh, L. H.: An Improved Concentration Test of Renal Function, J. A. M. A. **99**:1396-1398 (Oct. 22) 1932.

confined to the posterior aspect of the body and consisted of numerous small erythematous maculopapules arranged in groups over the upper part of the arms and back, together with many small erythematous follicular papules over the buttocks and thighs. The following morning, July 30, the blood thiocyanate concentration was 5.7 mg. per hundred cubic centimeters. By afternoon the eruption had become much more severe and extensive. Large urticarial wheals appeared

Fig. 2.—Thiocyanate dermatitis; the appearance on the eighth day of the eruption.

over the trunk, arms and lower part of the legs. The buttocks and thighs were covered with a brightly erythematous maculopapular exanthem. The cutaneous lesions were intensely pruritic and remained so throughout their course. The temperature was 100.2 F., and the conjunctivas were injected. Treatment with both phenobarbital and thiocyanate was discontinued, the patient having received a total of 6.17 Gm. of the latter.

The cutaneous lesions became still more severe, reaching their height on the fourth day after their appearance. The face was markedly flushed, the eyelids were edematous and conjunctivitis with lacrimation was present. There was some obstruction to breathing, due to nasal congestion. The patient complained of sore throat, became hoarse and had an irritative cough productive of small amounts of clear mucoid sputum. Examination of the nose and throat showed the mucous membrane to be pale and edematous. There was a feeling of tightness in the chest, with occasional bilateral pleuritic pain. Asthmatic attacks occurred several times. Anorexia was present together with annoying dysphagia. Burning on urination, headaches and generalized muscular aches added to the patient's discomfort. He was extremely weak. The systemic symptoms persisted throughout the course of the illness. The temperature was elevated to 99.2 to 100.8 F. daily until the eighteenth day of the eruption. The blood pressure dropped and remained at an average level of 150 systolic and 110 diastolic. The thiocyanate concentration of the blood fell slowly. A correlation of the clinical course of the reaction and the blood cyanate concentration is represented in figure 1.

The large urticarial lesions persisted for about a week. They then gradually became less erythematous, and their infiltration subsided. The appearance of the patient on the eighth day of the eruption is shown in the accompanying photograph (fig. 2). A rather pronounced, dull erythema persisted for a considerable time, similar to that seen in a fixed eruption. Exfoliation occurred after about two weeks. This was generalized over the body but consisted simply of shedding of the superficial epithelium over the individual lesions. Pigmentation and scaling were still present after three weeks. The patient's strength returned slowly, and he was still weak at the time of discharge, on August 19.

The patient was treated with bland lotions and cool spongings. The taking of fluids was encouraged. Nose drops containing ephedrine sulfate relieved the nasal congestion, and epinephrine hydrochloride given hypodermically controlled the asthmatic attacks. Codeine phosphate seemed to increase the pruritus. On August 8 the use of phenobarbital was resumed (0.032 Gm. four times daily) and was continued until the time of discharge without incident.

Repeated urinalyses revealed essentially the same findings as at the time of admission. A few granular casts persisted, but no hematuria occurred. On August 2, the fifth day of the eruption, the white blood cell count was 10,000 per cubic millimeter, and the differential count showed only 4 per cent eosinophils. However, on August 13, when the eruption was subsiding, the total white blood cell count was 11,700, with 46 per cent neutrophils, 18 per cent lymphocytes, 3 per cent monocytes and 32 per cent eosinophils.

COMMENT

We believe that there is no reasonable doubt that in this case the eruption was produced by thiocyanate. It did not resemble the usual type of phenobarbital dermatitis, and the patient later resumed the use of that drug, with no recurrence of the eruption.

The symptoms associated with this severe cutaneous reaction suggested that a generalized enanthem also occurred. As the reaction occurred at a blood concentration of thiocyanate well below that at which toxic symptoms occur in the average person, we are inclined to consider that the entire reaction was due to idiosyncrasy to the drug.

The patient's history, the urticarial character of the lesions, the pale edematous appearance of the nasal mucous membrane and the marked eosinophilia which developed are other points which indicate that the reaction was allergic in nature.

We wish to point out that a satisfactory fall in blood pressure occurred on the fifth day of thiocyanate therapy, when the concentration of thiocyanate in the blood was only 3.7 mg. per hundred cubic centimeters. This was an unusual effect with a blood level as low as that, and we believe that it indicated hypersensitivity of the vascular system also to the drug. If this unusual early drop in blood pressure had been interpreted as a danger signal, the severe reaction which followed might have been averted. This emphasizes the importance of careful daily determinations of the blood pressure as well as simultaneous studies of the thiocyanate level of the blood of patients receiving thiocyanate.

This case also emphasizes the point that thiocyanate should be given with caution to patients with a history of allergy and that its use should be discontinued immediately on the first appearance of any erythematous maculopapular eruption.

SUMMARY

A case of the severe urticarial type of dermatitis medicamentosa due to potassium thiocyanate has been presented. The clinical course of the reaction has been correlated with blood thiocyanate determinations. There was evidence which indicated that the reaction was allergic in nature and that the entire vascular system was involved.

LIPOID PNEUMONIA

REPORT OF TWO CASES

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Pneumonia due to the aspiration of oily preparations into the lungs was first described by Laughlen [1] in 1925. Subsequently other reports have appeared, so that in 1936 Ikeda [2] was able to collect 24 references to this condition.

Lipoid pneumonia usually occurs in debilitated infants or children, although its occurrence in adults has been described. In the majority of instances the patient suffers from some condition which makes occasional aspiration of materials from the pharynx practically inevitable. The substances which cause the trouble most frequently are nose drops and laxatives containing petrolatum. Cod liver oil, milk, and cream are responsible occasionally.

Lipoid pneumonia occurring in infants or children is referred to as the infantile type of the disease. In adults the pneumonia sometimes develops slowly over a period of years and forms a localized dense fibrous area. This is known as lipoid pneumonia of the adult type. In the majority of the cases, however, lipoid pneumonia in adults is of the infantile type.

Clinically, patients with lipoid pneumonia show the signs and symptoms of low grade pneumonia, with periodic exacerbations due to secondary infection. In cases of the adult type in which the pneumonia develops slowly to form a well circumscribed fibrotic area the disease may imitate chronic granulomatous pneumonia or tumor.

Roentgen examination shows areas of increased density, which in cases of extensive involvement show a tendency to affect both lungs, the right lung predominantly in the lower third of the upper lobe and the apex of the lower lobe, and the left lung in the middle third of the upper lobe and the apex of the lower lobe.[3] In cases of chronic involvement

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1. Laughlen, G. F.: Studies on Pneumonia Following Nasopharyngeal Injections of Oil, Am. J. Path. **1**:407, 1925.

2. Ikeda, K.: Lipoid Pneumonia of the Adult Type (Paraffinoma of the Lung): Report of Five Cases, Arch. Path. **23**:470 (April) 1937.

3. Reichle, H. S.: Bronchiogenic Distribution of Fluid and Particulate Matter: Its Site of Predilection and Mechanism of Transfer, Arch. Path. **25**:811 (June) 1938.

in adults the differentiation roentgenologically of this condition from neoplasm or unresolved pneumonia may be difficult.

At autopsy the lungs in the infantile type of lipoid pneumonia show evidence of reaction of the tissues to a foreign body plus the results of secondary invasion of bacteria. Grossly the consolidated lung tissue is a peculiar grayish yellow, and a cloudy, milky fluid containing minute oily droplets can be expressed from it. Microscopically the alveoli are filled with macrophages containing lipoids. Giant cells, more or less vacuolated, and lymphocytes are present. The septums show edema, fibrosis, infiltration by lymphocytes and spaces filled with lipoids. The adult type is considered to be fundamentally the same as the infantile type except that it is a late stage, being localized and densely fibrous.

The prognosis of the condition is usually poor, more because of the associated disease than because of the lipoid pneumonia itself.

Most of the patients with lipoid pneumonia encountered at the Cleveland City Hospital have been infants. In the past six months, however, 2 cases of lipoid pneumonia in adults have been observed clinically and at autopsy.

REPORT OF CASES

CASE 1.—H. K., a white woman aged 73, who entered the Cleveland City Hospital Oct. 18, 1938, had been in good health until September 15, since which time she had had a cough productive of small amounts of greenish white sputum. Dyspnea and a feeling of tightness in the chest were also present. The patient had allowed oily salve to "trickle down her throat," but she had not improved. A film of the chest taken October 13 showed moderately dense, coarse streaky mottling in the lower medial portion of the right lung field. This was interpreted as being due to a pneumonic process. The course subsequently was unfavorable, and the patient entered the hospital five days later.

Examination showed her to be dyspneic, cyanotic and acutely ill. There was evidence of severe chronic pulmonary emphysema. Coarse, raucous rales and wheezes were heard over both lungs. The temperature rose from 37 to 40 C. (98.6 to 104 F.), pulmonary edema developed, and the patient died in thirty-six hours.

Autopsy was done three hours after death. The lungs showed marked emphysema and chronic bronchitis. In the middle lobe of the right lung, near the hilus, there was an area of infiltration measuring 6.5 by 6.5 by 5 cm. This was sharply demarcated, granular and of a peculiar grayish yellow. The pulmonary lymph nodes were normal.

Microscopic examination of the area of consolidation showed numerous large vacuolated mononuclear cells in the alveoli and to a lesser degree in the septums. A few giant cells were present. Interspersed through the area were collections of lymphocytes and polymorphonuclear cells. The alveolar walls were thickened. The scarlet red stain showed fat in the vacuolated cells. In addition, there was some fat free in the alveoli and septums.

The only other important pathologic observations were acute pneumococcic ethmoiditis and sphenoidal sinusitis.

CASE 2.—G. C., a white man aged 66, who entered the Cleveland City Hospital Nov. 10, 1938, had a carcinoma of the esophagus. A Janeway gastrostomy was

done on November 25, and the patient had an uneventful convalescence, oral feedings being resumed on the second postoperative day. Roentgen therapy was started December 20, a daily dose of 300 r being administered to both sides of the chest wall anteriorly and posteriorly. The patient's general condition at this time was good. He had moderate difficulty in swallowing, but oral feeding still seemed feasible. His food consisted of a soft diet, with liberal amounts of milk and cream, and he received in addition 30 cc. of an emulsion of liquid petrolatum and agar (plain petrolagar) twice a day and 4 cc. of cod liver oil three times a day.

On Jan. 1, 1939, fever and symptoms referable to the respiratory system appeared. On January 5 a fluoroscopic and roentgen study of the chest showed streaked mottling extending outward from the hilus of the left lung. It was thought that the patient had bronchopneumonia and probably mediastinitis.

Subsequently the patient was weak and lethargic and coughed considerably. The temperature varied between 38 and 39.5 C. (100.4 to 103.1 F.). Roentgen therapy was discontinued January 23, a total of 2,100 r having been given to each of the four portals. The patient's condition, however, remained unchanged.

On the morning of February 2 his condition, although poor, was virtually as it had been for the previous month except that he was expectorating small amounts of dark blood. Two hours later a large amount of blood suddenly welled out of his mouth and nose, and he died almost at once.

Postmortem examination, done seven hours after death, showed a tumor involving the esophagus at the level of the bifurcation of the trachea. The tumor had eroded into the aorta, there being a fistula between the esophagus and the aorta. There were large amounts of blood in the trachea, the stomach and the upper part of the small intestine.

The upper half of the lower lobe of the left lung was consolidated. The cut surface was smooth, firm and pale yellowish gray. The remaining portions of the lungs showed no significant abnormalities. There was no fistula between the esophagus and the trachea or bronchi. The pulmonary lymph nodes were normal.

Microscopic examination of the area of pneumonia in the upper portion of the lower lobe of the left lung showed the lung to be practically airless. The alveoli contained many vacuolated phagocytic cells in addition to moderate numbers of lymphocytes and polymorphonuclear cells. A few vacuolated multinucleated foreign body giant cells were present. In a few areas there was early organization of the exudate. The alveolar walls were thickened and in some areas contained fibroblasts in addition to cells similar to those found in the alveoli.

The scarlet red stain showed large amounts of free and phagocytosed fat in the alveoli and interstitial tissue.

COMMENT

In cases of lipoid pneumonia oil usually enters the lungs because of some serious disease which makes aspiration of material from the pharynx practically unavoidable. In case 1, however, there was no such explanation, oil having entered the lungs because of the patient's habit of intentionally letting oily salve trickle down her throat. The hazard of such a procedure is shown by the fact that the clinical course and pathologic observations indicate that the lipoid pneumonia was an important factor in the patient's death.

The lipoid pneumonia in this case was of the infantile type, and from the clinical standpoint it is known that the pneumonia must have

been of recent origin, because the use of oil did not extend over a period of more than one month before death occurred. That early lipoid pneumonia in the adult is indistinguishable from the infantile type has been emphasized by Ikeda.[2] The area of pneumonia becomes fibrotic and localized to form a tumor-like mass only with the passage of time. In this case, however, the patient died before such changes could occur.

The second case is less unusual in regard to the manner in which oil entered the lungs. It seems probable that dysphagia incident to the carcinoma of the esophagus resulted in aspiration into the lungs of material intended to pass down the esophagus. The material no doubt entered the lungs by way of the larynx, because autopsy revealed no fistula between the esophagus and the trachea or bronchi. The exact etiologic agent in this case is not clear, since the patient received several oily substances which might have been responsible. The exposure lasted about two months, and from a pathologic standpoint the case affords further evidence that lipoid pneumonia in its early stages in the adult is fundamentally the same as the infantile type. The early organization of the exudate indicates, however, that the pneumonia in this case was approaching an intermediate stage between the infantile and the adult type.

SUMMARY

Two cases of lipoid pneumonia in adults indicate the hazard of introduction of oily materials into the pharynx under conditions in which aspiration of the material may occur. In 1 instance oil entered the lungs owing to the patient's habit of letting oily salve trickle down her throat, and in the other case oil entered the lungs as a result of dysphagia due to esophageal obstruction. The cases also illustrate that the early stages of lipoid pneumonia in the adult are indistinguishable pathologically from the infantile type of the disease.

Progress in Internal Medicine

VASCULAR DISEASES

A REVIEW OF SOME OF THE RECENT LITERATURE, WITH A CRITICAL REVIEW OF THE SURGICAL TREATMENT

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A REVIEW OF SOME OF THE RECENT LITERATURE

By Dr. Scupham and Dr. Van Dellen

Many reports of academic and practical value have been published during the past year. We have endeavored, as far as possible, to include for consideration only those articles which contributed new information or those which seemed of importance because they supplemented or confirmed present beliefs. An attempt was also made to evaluate certain controversial data reported on related subjects by various authors. Considerable space has been devoted to hypertension because of the increasing interest in it shown by the numerous contributions on this subject.

PHYSIOLOGY

Grant and Holling [1] made additional studies on the differences between the vascular responses of the proximal and the distal parts of the human limbs. Recent observations have revealed that while warming of the body provokes a large increase in blood flow and cutaneous temperature in the hands and feet, it causes no more than a slight rise in blood flow and cutaneous temperature in the proximal parts of the extremities. Neither flushing nor warming of the skin of the proximal portion occurs if the circulation to the extremity has been arrested.

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1. Grant, R. T., and Holling, H. E.: Further Observations of the Vascular Responses of the Human Limb to Body Warming: Evidence for Sympathetic Vasodilator Nerves in the Normal Subject, Clin. Sc. **3**:273, 1938.

This variation has been explained as being due to the differences in the distribution of the arteriovenous anastomoses. The persons tested were subjected to strong warming of the body, accomplished by immersing two or three extremities in water maintained at 45 to 46 C. with all portions of the body completely covered except the face and the limb under observation. Blood flow and cutaneous temperature were measured by methods previously described. It was found that when warming of the body was pushed to excess in this manner vasodilatation developed in the proximal areas of the extremities. Observations were made on several patients before and after sympathetic ganglionectomy and on several subjects following nerve block. Following surgical operations the blood flow was increased but soon diminished so that it returned almost to the preoperative level within a week. Strongly warming the body at this time failed to provoke the vasodilatation observed before operation. Similar responses were noted over the anesthetized skin of the arm and leg after nerve block. The authors expressed the opinion that these observations demonstrated that the vasodilatation provoked in the arm and leg by heating the body was dependent on the integrity of the sympathetic nerves, as was already demonstrated for the hand and foot. The results obtained from these and previous observations were interpreted as indicating two means of defense against rise in body temperature. The first is brought into action by relatively gentle heating and consists chiefly of dilatation of the arteriovenous anastomoses in the extremities through inhibition of vasoconstrictor tone. The second occurs when the heating is more intense and consists mainly in general dilatation of the cutaneous vessels associated with sweating. The vasodilatation produced in the proximal part of the extremity was brought about by stimulation of cutaneous sympathetic nerves.

Fatheree and Allen,[2] while investigating the mechanism of indirect vasodilatation, corroborated the existing views on this subject. They demonstrated that indirect vasodilatation induced by warming an extremity depended on the return of blood from the warmed extremity to the general circulation. In addition it was shown that the occurrence of indirect vasodilatation in a digit depended on the integrity of its sympathetic nerve supply. They were able to present evidence demonstrating the presence of vasodilator nerves in the lower extremities in 2 cases of Raynaud's disease. Keeping the feet in a cool environment, they showed that a regional nerve block of the lower extremity prevented induction of indirect vasodilatation by heat in the anesthetized

2. Fatheree, T. J., and Allen, E. V.: Sympathetic Vasodilator Fibers in the Upper and Lower Extremities: Observations Concerning the Mechanism of Indirect Vasodilation Induced by Heat, Arch. Int. Med. **62**:1015 (Dec.) 1938.

areas while vasodilatation was occurring in the unanesthetized areas of the same foot. They were unable to demonstrate the presence of sympathetic vasodilator fibers in normal persons by this method.

Atlas [3] studied the cutaneous temperature of a patient who had a complete traumatic division of the peripheral nerves to the left arm. He noted that the response in cutaneous temperature was similar to that seen after cervicothoracic sympathetic ganglionectomy when the postganglionic fibers were sectioned. He was able to demonstrate the phenomenon of increased sensitivity of the blood vessels to epinephrine as a cause of vasoconstriction. He suggested this as the possible explanation of the vasomotor and nutritional changes in denervated tissue. Grant and Holling,[1] in a study of a similar case, in which the right external popliteal nerve was accidentally severed, were unable to induce indirect vasodilatation in the extremity in a cool environment. The best explanation for this phenomenon was thought to be furnished by the destruction of the vasodilator fibers. There is an increasing tendency to regard this explanation as correct.

Wells, Youmans and Miller [4] measured pressure in the muscle as well as in the superficial tissue. They confined their studies chiefly to observations on normal subjects. The tissues of the leg were chosen because of the failure of edema to develop in the legs of normal persons on prolonged quiet standing. They noted that the pressure in the leg muscles which were tightly covered with fascia rose to 50 cm. of water or higher during prolonged venous congestion. They expressed the belief that pressures of this magnitude probably were sufficient to stop filtration into these muscles during quiet standing. In muscles loosely covered, such as the gastrocnemius, the pressure did not rise above 20 cm. of water during congestion. They showed that the intramuscular pressure was affected independently by several factors, of which the most important were: the lightness of the fascia, the amount of intravascular and extravascular fluid present and the components of contractile force of the muscle. Maximal voluntary contractions of various muscles elevated intramuscular pressure to values ranging from 10 to 118 cm. of water. As such pressures in most muscles are lower than the level of diastolic arterial pressure, blood flow through these muscles cannot be stopped during ordinary contractions. The leg volume continued to increase indefinitely during quiet standing. In each case the ratio of the final

3. Atlas, L. N.: The Etiology of Vasomotor and Nutritional Changes Following Peripheral Nerve Section, Surgery **4**:718, 1938.

4. Wells, H. S.; Youmans, J. B., and Miller, D. G., Jr.: Tissue Pressure (Intracutaneous, Subcutaneous, and Intramuscular) as Related to Venous Pressure, Capillary Filtration, and Other Factors, J. Clin. Investigation **17**:489, (July) 1938.

rate of filtration to the initial rate was of the magnitude to be expected on the assumption that filtration ceases in muscles under high pressure but continues indefinitely in the skin and gastrocnemius, the low pressure filtering areas. They did not assume that fluid left the leg through lymphatics during quiet standing.

Sodeman and Burch [5] described a simple and accurate method for measuring the distensibility of skin. Horizontal stretching of the skin of a limb after the limb has been placed in a standard position is easily accomplished with a small caliper of known calibration. The normal mean values for the pretibial area, the dorsum of the foot, the midline of the abdomen below the umbilicus, the volar surface of the forearm and the dorsum of the hand were found to be 0.31, 0.59, 2.07, 0.93 and 1.34 mm. per cubic millimeter per hundred grams, respectively. The regional variations disclosed less distensible skin in the lower extremities.

Edema, certain vascular diseases and some dermatoses were found to produce changes in the normal distensibility of the skin. As edema progresses the distensibility decreases, and with recession of the edema the distensibility tends to return to a normal range. The loss of distensibility was found to be an important factor in limiting the formation of edema. In urticaria, senile atrophy, occupational atrophy, allergic eczema and scleroderma, definite changes in the distensibility of skin were observed which correlated with the clinical state of the patient.

Blood Flow.—The rate of blood flow in the normal finger was studied by Wilkins, Doupe and Newman.[6] The method of Hewlett and Van Zwaluwennburg was adapted, and measurements were made on a small plethysmograph carefully fitted to the last two phalanges of the finger. The rate of blood flow to the finger was found to range from 0.02 cc. per minute per 10 cc. when the peripheral vessels were constricted to 12 cc. when they were dilated. These figures showed that the blood flow to the normal finger may be increased as much as a hundred times during vasodilatation induced by warming of the body. When the vessels are already dilated, the flow may be temporarily decreased as much as twenty times following a vasoconstricting stimulus. They demonstrated also that the increase in blood flow resulting from local heating of the finger was not as great as that produced by warming of the body. The blood flow to the terminal phalanx was found to be greater than that to the middle phalanx of the finger when the vessels were dilated.

5. Sodeman, W. A., and Burch, G. E.: A Direct Method for the Estimation of Skin Distensibility with Its Application to the Study of Vascular States, J. Clin. Investigation **17**:785 (Nov.) 1938.

6. Wilkins, R. W.; Doupe, J., and Newman, H. W.: The Rate of Blood Flow in Normal Fingers, Clin. Sc. **3**:403 (Dec.) 1938.

Stead and Kunkel [7] described a plethysmographic method for measuring quantitatively the blood flow in the foot. With a standard correction for the inertia of the plethysmograph and a bellows system, the instrumental error was found to be 3 per cent. Using this plethysmograph, they [8] studied the blood flow in the normal foot. The flow was recorded as the cubic centimeters of blood per minute per hundred cubic centimeters of tissue. Studies were made at 43 C., and the flow at this temperature was designated as the maximal flow. The average maximal flow in thirty-four normal persons was 17.1 cc., with the highest 25.9 cc. and the lowest 11.1 cc. The values were lower for males than for females, the averages being 16.3 cc. for the former and 18.7 cc. for the latter. In the presence of a normal cardiovascular system the blood flow showed no appreciable decrease with age. The average difference between the maximal flow in the right and that in the left foot was 1.8 cc. Simultaneous readings on one hand and one foot revealed the average flow of the hand to be 32 cc. and that of the foot 15.7 cc. These measurements are indicative of the considerably smaller reserve of blood in the foot as compared with that in the hand.

In arteriosclerosis and thromboangiitis obliterans the maximal blood flow to the foot was reduced 50 per cent without symptoms or trophic disturbances. When the flow was reduced to one-third the normal value, or to the level of 5 cc. or below, symptoms or trophic disturbances usually were present. In both arteriosclerosis and thromboangiitis obliterans severe intermittent claudication in the calf was in some patients incapacitating, though the blood flow in the foot was as great as in many normal persons. Thus the presence of an adequate supply of blood to the foot did not eliminate the possibility of obliterative disease involving the vessels of the calf muscles. This is in keeping with observations reported last year.

Continuing their studies with the plethysmograph, Kunkel, Stead and Weiss [9] compared the blood flow and vasomotor reactions of the hand and foot with those of the forearm and calf. This seemed necessary because of the wide variations in the proportion of muscle to skin in these parts and because of the presence of numerous arteriovenous anastomoses in the skin of the hands and feet. Following strong

7. Stead, E. A., and Kunkel, P.: A Plethysmographic Method for the Quantitative Measurement of the Blood Flow in the Foot, J. Clin. Investigation **17**:711, 1938.

8. Kunkel, P., and Stead, E. A.: Blood Flow and Vasomotor Reactions in the Foot in Health, in Arteriosclerosis and in Thromboangiitis Obliterans, J. Clin. Investigation **17**:715, 1938.

9. Kunkel, P.; Stead, E. A., and Weiss, S.: Blood Flow and Vasomotor Reactions in the Hand, Forearm, Foot, and Calf in Response to Physical and Chemical Stimuli, J. Clin. Investigation **18**:225 (March) 1939.

sensory stimulation, the forearm and calf responded in three ways: (1) by a decrease in volume after a latent period of from three to nine seconds, (2) by an increase in volume after a latent period not exceeding two seconds and (3) by a biphasic response—first an increase in volume with a short latent period, usually not exceeding two seconds, and subsequently a decrease in volume. The authors were of the opinion that an active reflex vasoconstriction took place in cases in which a decrease in volume occurred. In cases in which an increase in volume occurred it was believed to be the result of a transient increase in cardiac output and a passive distention of the vascular bed. Numerous variations in response were noted not only in different persons but also in the same persons. The vessels in the upper extremities were more sensitive than those in the lower. Constrictor responses of the forearm and calf paralleled the vasoconstrictor reactions which have been shown to occur in the hand and foot following similar sensory stimulation. The intensity of the reactions had to be greater to produce vasomotor responses in the forearm and calf as compared with the hand and foot. The blood flow was greater in the hand and foot than in the forearm and calf when induced by local heat of 43 C. Local heat of the same degree produced complete vasodilatation in the skin but relatively slight dilatation in the underlying muscles, whereas exercise had the opposite effect, producing dilatation in the muscles but not in the skin. The latter observation was not influenced by variations in external temperature. Epinephrine, 1 cc. of a 1 1:000 solution injected subcutaneously, caused a marked decrease in blood flow in the hand and foot and a moderate increase in blood flow in the foramen and calf. Pitressin (betahypophamine), 1 cc. injected intramuscularly, caused a decrease in flow in the hand and foot, as did epinephrine. It also caused a moderate decrease in flow in the forearm and calf. Neither of these drugs interfered with the dilatation of the vessels in the muscles in response to exercise or induced arterial occlusion.

The standard technic for using the same type of plethysmograph was described in detail by Abramson, Zazeela and Marrus.[10] Numerous mechanical and physical difficulties were mentioned, especially those concerned with the position of the lower extremity, the position of the cuff, occlusion pressure, air in the apparatus, calibrations and the diameter of the glass tube of the recording apparatus. In their second article[11] various physiologic factors were discussed in relation to the

10. Abramson, D. I.; Zazeela, H., and Marrus, J.: Plethysmographic Studies of Peripheral Blood Flow in Man: I. Criteria for Obtaining Accurate Plethysmographic Data, Am. Heart J. **17**:194 (Feb.) 1939.

11. Abramson, D. I.; Zazeela, H., and Marrus, J.: II. Physiologic Factors Affecting Resting Blood Flow in the Extremities, Am. Heart J. **17**:206 (Feb.) 1939.

blood flow. Normal values, somewhat lower than those of Kunkel and Stead, were obtained. They found that the hands were more difficult to control than the feet, because they were more easily subjected to spontaneous vasomotor changes. In a number of persons they observed a slight drop below the base line in the blood flow of the lower extremities after the release of the occlusive pressure. This appeared to have its origin in a local reflex, as it was independent of the amount of pressure used and a paravertebral block failed to abolish it. Studies were also made on persons with various bilateral maladies. In a patient with increased venous pressure in the right arm, the flow in this arm was found to be definitely increased as compared with that in the other. Little difference in blood flow was noticed in the two arms of a person with unilateral hypertension. Decreased blood flow was noted in a person during sleep and in another who went into shock following an injection of "spasmalgin," a proprietary preparation containing derivatives of atropine, opium and papaverine.

Using a new and sensitive photoelectric recording type of plethysmograph, Martin, Marcellus and Sykowski [12] studied the coincidental synchronous respiratory waves. They found them to be of mechanical origin and due essentially to the increase in pressure in the thoracic and abdominal vessels with each respiration. They believed that this pressure was transmitted to the extremities. They noted that the magnitude of the waves of respiration was dependent on the patency of the arterial bed, decreasing in size with vasoconstriction and increasing with vasodilatation. They suggested that changes in this magnitude be studied along with those in pulse rate and pulse volume in the digits. This article and others on this subject demonstrate the difficulties and pitfalls of this method of study.

The details of the photoelectric plethysmograph devised by Hertzman [13] were described in last year's review. In a recent article Hertzman discussed the numerous sources of error involved in the quantitation of the cutaneous plethysmogram, especially those bearing on the problem of the blood equivalent and on the quantitative accuracy of this device. Errors occur through movements of the skin, through the presence of a large artery in the immediate neighborhood of the area observed and through improper contact of the plethysmograph with the skin. Readings cannot be obtained over the trunk, as the movement of the skin over this area cannot be controlled. The possibility of distant or deeper tissues influencing the recording of the pulse is discussed but is con-

12. Martin, S. J.; Marcellus, F. S., and Sykowski, P.: Plethysmographic Studies with Special Reference to Waves of Respiration, J. Lab. & Clin. Med. **24**:111, 1938.

13. Hertzman, A. B.: The Blood Supply of Various Skin Areas as Estimated by the Photoelectric Plethysmograph, Am. J. Physiol. **124**:328 (Nov.) 1938.

sidered of little significance. The importance of a constant source of light is stressed. Simultaneous photoelectric and mechanical plethysmograms of the fingers were compared, and the various vascular responses to some of the common procedures were recorded to establish the validity of the photoelectric plethysmograph. The argument was advanced and supported by suitable data that with normal circulatory dynamics and under resting conditions the volume pulse of an area of skin was a measure of the richness of the arterial blood supply of that area. The finger pad was found to have the most abundant arterial supply. Next in order of frequency were the ear lobe, toe pad, palm of the hand, skin of the forehead and face, dorsa of the finger, hand and foot, forearm, knee and tibia. Readings were made during various seasons, and the highest readings were obtained in the summer. Hertzman was unable to demonstrate that the difference in vasomotor reactions in various areas depended solely on richness of arterial supply, as he observed a surprising seasonal constancy in pulse volume in the forehead, nose, forearm and dorsa of the hand and foot in contrast to the dilatation in warm weather in the finger pad, toe pad and ear.

Mendlowitz [14] studied the blood flow in clubbed fingers on patients with diverse pathologic conditions. The maximum heat elimination was used as an index of blood flow. The various responses of the blood vessels to changes in environmental temperatures were found to be within normal limits. In patients with clubbing of the fingers secondary to pulmonary or to congenital cardiac disease the blood flow of the distal phalanges was increased. In the same patients pressure was increased in the digital but decreased in the brachial-digital arteries. In patients with hereditary clubbing these pressures and gradients were normal. In patients with unilateral clubbing the blood flow of the involved finger tips may or may not be increased or decreased. In these patients no significant change was found in blood pressure gradients.

Scull [15] described a new method of visualizing changes in pressure and volume for the study of variations in peripheral circulation. He utilized the phenomenon that a pattern of light and dark bands appears when pressure is applied to an ordinary glass cover slip rigidly fixed to a microscopic slide. This is due to the interference of light waves associated with reflecting surfaces separated by a thin layer of air of nonuniform thickness. When the pressure applied varies, the thickness of air is modified, which in turn alters the interference pattern. He

14. Mendlowitz, M.: Some Observations on Clubbed Fingers, Clin. Sc. **3**:387 (Dec.) 1938.

15. Scull, C. W.: A Simple Method for Visualizing Pressure and Volume Changes Applicable to Observations on the Rhythmic Variations in the Peripheral Circulation, J. Lab. & Clin. Med. **24**:753 (April) 1939.

applied this simple apparatus to the radial artery or to the finger, and with each pulsation various movements of the band of light were produced. Obstructing the flow of blood resulted in prompt cessation of the movement of these bands. He suggested that this apparatus be used for purposes served by other oscillometric and sphygmoscopic devices. Considerable refinement appeared to be necessary. The main objection was that a permanent record of data could not be obtained.

Bazett [16] contrasted the effects on blood volume and circulation of high temperatures applied in acute experiments or in treatments of short duration with those of milder temperatures applied chronically for days. In the analysis of the effects of heat it was necessary to distinguish the parts played by: (*a*) local dilatation in the cutaneous vessels, with the accompanying local increase in rate of flow, capillary pressure and fluid transudation; (*b*) compensatory reduction of the vascular bed in areas other than the skin, which allows dilatation in the cutaneous vessels even when the blood volume is unchanged or reduced; (*c*) increases in blood volume on exposure to heat, which form an alternative method of compensation in lieu of vasoconstriction, and (*d*) alterations in cardiac output.

The part played by each of these factors was discussed in detail. Particular attention was given to blood volume and its effect on the cardiovascular system. Experiments with a moderate, steadily maintained rise in environmental temperature, similar to that present during the summer, revealed a significant increase in blood volume, which apparently was an adaptation to the prolonged peripheral vasodilatation produced by exposure to moderate heat over a period of days. The author was doubtful whether changes in blood volume could be produced by fluctuating temperatures.

Temperature of Skin.—Opinions appear to vary as to the changes in the cutaneous temperature of the extremities produced by changes in posture. Roth, Williams and Sheard [17] noted an increase in cutaneous temperature when the subjects were in an upright position and a decrease when the legs were elevated. They attributed these alterations in temperature to changes in the peripheral circulation as a result of changes in hydrostatic pressure. Their observations were in keeping with those previously reported by other authors of a decrease in the velocity of blood flow, an increase in the venous pressure and an average increase of about 4 per cent in the volume of the lower extremities as measured by the plethysmograph while the legs were in a dependent position.

16. Bazett, H. C.: The Effect of Heat on the Blood Volume and Circulation, J. A. M. A. **111**:1841 (Nov. 12) 1938.

17. Roth, G. M.; Williams, M. M. D., and Sheard, C.: Changes in Skin Temperatures of the Extremities Produced by Changes in Posture, Am. J. Physiol. **124**:161 (Oct.) 1938.

Mayerson and Toth,[18] on the other hand, noted a decrease in both the surface and the subcutaneous temperatures of subjects who were suddenly changed to an upright position. They attributed this decrease to compensatory vasoconstriction as a normal adjustment to the upper extremities. They expressed the opinion that their findings were in keeping with those of Hill and Barnard, who noted similar vasoconstriction in the splanchnic area. Roth, Williams and Sheard [17] and Mayerson and Toth [18] reported on persons observed under similar basal conditions, using equally sensitive thermocouples. It is difficult to explain their opposite results. Roth, Williams and Sheard had their subjects standing on blankets, clothed in light pajamas and tilted at angles of 15 and 20 degrees (most favorable position for vasodilatation), whereas Mayerson and Toth used nude subjects suspended on a tilting table at angles of more than 60 degrees. In the latter group syncope was not uncommon. In addition, simultaneous subcutaneous temperatures were taken and studies of blood pressure were made. The method used by Mayerson and Toth was certainly more conducive to vasoconstriction. In addition, tilting patients as the latter authors did must certainly influence all of the compensatory mechanisms regulating blood pressure.

Freeman and Nickerson [19] observed the cutaneous and rectal temperatures of normal subjects exposed to different environmental temperatures for two hours—10 subjects were exposed to a temperature of 68 F. and an equal number to a temperature of 59 F. At both 59 and 68 F. the cutaneous temperatures fell markedly, more rapidly in the first hour and more precipitously at 59 than at 68 F. The fall was the least on the forehead and greatest on the extremities. The rectal temperature showed little change for an hour, but after that it began to fall, more rapidly at 68 than at 59 F. There was a significant individual variation as to the temperature levels. The difference was greatest in the extremities. The rate at which the cutaneous temperature fell was independent of the initial level of the rectal temperature and only slightly influenced by the initial cutaneous temperature. The average levels of cutaneous and rectal temperatures were slightly related to each other but in an opposite direction.

Circulation Time.—Mayerson, Sweeney and Toth [20] studied the influence of posture on the circulation time. They used the method of

18. Mayerson, H. S., and Toth, L. A.: The Influence of Posture on Skin and Subcutaneous Temperatures, Am. J. Physiol. **125**:474 (March) 1939.

19. Freeman, H., and Nickerson, R. F.: Skin and Body Temperatures of Normal Individuals Under Cold Conditions, J. Nutrition **15**:597 (June) 1938.

20. Mayerson, H. S.; Sweeney, H. M., and Toth, L. A.: The Influence of Posture on Circulation Time, Am. J. Physiol. **125**:481 (March) 1939.

Spier, Wright and Saylor. The solution was injected into the leg veins, and a greatly increased time was noted with the subject in an upright position. In some cases readings could not be obtained. They came to the conclusion that the slowing was due to stagnation or pooling of the blood in the veins of the extremities.

Capillaries.—Brewer [21] was able to demonstrate rhythmic changes in the capillaries of the skin associated with the cyclic menstrual rhythm. These changes consisted essentially of changes in capillary fragility. He was able to produce capillary hemorrhages with greater ease during the few days prior to and on the first day of menstruation than during the remainder of the cycle. He expressed the opinion that these changes were a direct result of vascular spasm and suggested that menstruation was not a local but a generalized vascular phenomenon. There is no evidence to date indicating that vasospasm is related to increased capillary fragility.

White and Jones [22] studied the rate of filtration through the capillary walls in various pathologic and control sites. They used a pressure plethysmograph after the methods of Landis and Gibbons, regulating it after the method of Smirk. Obstructing venous pressures were used which were greater in each case by a constant amount than the colloid osmotic pressure of the serum. The range of readings observed in normal controls was very wide and was not significantly exceeded in any of the pathologic states studied.

Leydhecker [23] found little relationship between the capillaries in the nail bed and those of the eyes. In only 7 of 31 patients were the findings significant. As these 7 patients were over 40 years of age, he was unable to come to any definite conclusions. A definite relationship was noted by Gifford and Marquardt in certain vasospastic phenomena. Their contribution will be discussed under "Angiospastic Disturbances," page 613.

Oscillometry.—A new recording oscillometer was described by Friedman, Ott and Oughterson.[24] It was found suitable for precise measurements of the vascular pulsations in the toes and finger tips.

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21. Brewer, J. I.: Rhythmic Changes in the Skin Capillaries and Their Relation to Menstruation, Am. J. Obst. & Gynec. **36**:597 (Oct.) 1938.

22. White, B., and Jones, C. M.: The Rate of Filtration Through the Capillary Walls as Measured by the Pressure Plethysmograph: Observations on Control Subjects and on Patients with Intrahepatic Disease, Thyrotoxicosis and Myxedema, J. Clin. Investigation **18**:73 (Jan.) 1939.

23. Leydhecker, F. K.: Capillaruntersuchungen am Fingernagelsaum von Augenkranken, Arch. f. Ophth. **139**:97, 1938.

24. Friedman, I.; Ott, L. H., and Oughterson, A. W.: A New Sensitive Recording Oscillometer, Am. Heart J. **16**:575 (Nov.) 1938.

Action of Drugs.—Perlow [25] studied the effect of prostigmin on the temperatures of the skin in 1 normal man and 2 women with mild vasospastic phenomena. The prostigmin was given in doses of 0.5 mg. subcutaneously and in doses of 15 mg. by mouth. With both methods of administration a rise in temperature was noted, higher when the drug was given by mouth. The response was not as great as after a peripheral nerve block. A histamine skin test evoked a reaction of increased intensity following administration of prostigmin. These studies indicated to the author that prostigmin produced arterial rather than arteriolar or capillary dilatation.

Littauer and Wright [26] were unable to secure as much vasodilatation with papaverine hydrochloride as with the simple procedure of immersion in water for the same purpose. The papaverine hydrochloride was given intravenously in doses of 0.03 Gm. (½ grain) or more. The temperature of the skin was used as an index of vasodilatation. Two normal persons as well as a number with peripheral vascular diseases were studied. Blood pressure readings were taken simultaneously. They were found to be slightly lowered. In a few instances capillary changes were noted with the capillary microscope. Color changes seldom occurred. It is unfortunate that in these studies cutaneous temperature was the sole index of vasodilatation observed. Other methods, such as oscillometry, might have shown evidence of vasodilatation, as these results are not in keeping with other current clinical reports.

Saland [27] noted the effect of benzedrine sulfate and cigarets on a small group of normal persons and patients suffering from occlusive types of vascular diseases. Following ingestion of benzedrine sulfate, a drop in cutaneous temperature was noted along with a rise in blood pressure and a slowing of the pulse. Observations on cutaneous temperature following smoking were found inconstant. Helmer, Kohlstaedt and Page [28] isolated nicotine from the urine of persons who smoked. Its pharmacologic properties were the same as those of pure nicotine. They found that most of the nicotine disappeared from the urine within three or four days after smoking was discontinued. Nicotine appeared to be the substance responsible for the marked pressor action of many specimens of urine. They noted that unless tobacco was

25. Perlow, S.: Vasodilating Action of Prostigmin, J. Pharmacol. & Exper. Therap. **66**:66 (May) 1939.

26. Littauer, D., and Wright, I. S.: Papaverine Hydrochloride: Its Questionable Value as a Vasodilating Agent for Use in the Treatment of Peripheral Vascular Diseases, Am. Heart J. **17**:325 (March) 1939.

27. Saland, G.: Benzedrine Sulfate and Cigarettes: Effect on Skin Surface Temperature, New York State J. Med. **38**:1462 (Nov. 15) 1938.

28. Helmer, O. M.; Kohlstaedt, K. G., and Page, I. H.: Isolation of Nicotine from Human Urine, Am. Heart J. **17**:15 (Jan.) 1939.

eliminated as a source of pressor substance in urine, conclusions relating urinary pressor substances to arterial disease are not justifiable. It was suggested that nicotine might be retained by the body when there is a decrease in renal function.

Scarborough and Stewart [29] were able to reduce the number of hemorrhages in patients with vitamin deficiencies by oral administration of hesperidin (vitamin P). This effect was observed when petechial hemorrhages were induced by application of pressure and in cases in which spontaneous hemorrhages were observed after administration of preparations of arsenic or bismuth. The authors expressed the opinion that the hemorrhagic tendencies in these cases were independent of the presence of ascorbic acid in the diet.

Roome [30] studied in dogs the effect of small doses of epinephrine on the blood flow in the femoral artery. The studies were done with a strohmuhr. The most frequent type of response was a combined dilatation and constriction with a variation of these two phases in their time relationship according to the rate of flow. No pure dilator effects were observed. He expressed the belief that the site of dilatation was in the capillaries and that the site of constriction was in the arterioles and arteries.

The vasodilating effect of nicotinic acid was noted by Spies, Bean and Stone [31] incidental to their study of this drug on pellagra. Following oral or intravenous administration of nicotinic acid, flushing, burning, itching and a sensation of increased local heat in the skin were noted. Definite increases in temperature of the skin of the face, neck and trunk were recorded, with no change or a lowering in the temperature readings for the hands and feet. The similarity of the drug to histamine when given intracutaneously was noted. Acetylcholine was found to be destroyed more rapidly than nicotinic acid, although both gave similar cutaneous responses.

Fellinger and Schweitzer [32] reported the clinical histories of 3 patients in whom severe vascular impairments developed in connection with mercury poisoning. It was impossible to make anatomic studies on the vessels of these patients, but the clinical manifestations of the vascular lesions resembled those of the various forms of obliterating endarteritis; however, in their unusually rapid, almost fulminating course they differed from idiopathic vascular diseases.

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29. Scarborough, H., and Stewart, C. P.: Effect of Hesperidin (Vitamin P) on Capillary Fragility, Lancet **2**:610 (Sept. 10) 1938.

30. Roome, N. W.: The Effects of Intra-Arterial Epinephrin on the Blood Flow in an Extremity, Am. J. Physiol. **123**:543 (Sept.) 1939.

31. Spies, T. D.; Bean, W. B., and Stone, R. E.: The Treatment of Subclinical and Clinical Pellagra, J. A. M. A. **111**:584 (Aug. 13) 1938.

32. Fellinger, K., and Schweitzer, F.: Vascular Diseases After Poisoning with Mercury, Arch. f. Gewerbepath. u. Gewerbehyg. **9**:269 (Dec.) 1938.

Maijala [33] reported the death of a patient following subcutaneous administration of 0.8 mg. of histamine. As this patient had syphilitic aortitis with obstruction of the coronary orifices, the author cautions against the use of this drug in patients with this type of disorder.

THROMBOANGIITIS OBLITERANS

Westcott and Wright [34] studied the problem of specific hypersensitiveness of the skin to tobacco in 35 cases of thromboangiitis obliterans and 36 control cases. In all cases in which marked reactions to tobacco were shown, passive transfer studies were made. They concluded that patients with thromboangiitis obliterans did not show a higher incidence of positive cutaneous reactions than the control group, positive reactions being found in 42.8 per cent of the former and 48 per cent of the latter. They expressed the belief that the discrepancies apparent in the reports of various authors were probably due to erroneous interpretation, as the chemical irritation of tobacco may produce many nonspecific reactions. Harkavy,[35] on the other hand, found sensitivity to tobacco in 70 per cent of a large series of cases. He studied 12 cases in detail, in 10 of which thromboangiitis obliterans was present, in 1 migrating phlebitis and in 1 acute thrombosis. He made biopsies on immediate and delayed skin reactions to injected tobacco and to injected saline solution as a control. Histologic sections of the immediately occurring urticarial wheals showed eosinophils in varying number. In 3 cases in which delayed reactions were noted an acute dermatitis was found. The exciting role of tobacco in the 12 cases studied was, in addition, corroborated clinically by the arrest in the progress of the symptoms following cessation of the use of tobacco.

Boyd [36] studied 25 cases of thromboangiitis obliterans. He was able to divide this condition clinically into a proximal and a distal type. In the proximal type the initial symptom was intermittent claudication of vessels in the calf muscles with marked postural changes and absence of pulsations in the larger vessels. Arteriographic and pathologic study revealed that the disease process affected the main vessels. Histologically, the pathologic picture differed from Buerger's original description in that the thrombosis appeared to occur as a primary event

33. Maijala, P.: Death Due to Histamine, Nord. med. tidskr. **16**:1287 (Aug.) 1938.

34. Westcott, F. H., and Wright, I. S.: Tobacco Allergy and Thromboangiitis Obliterans, J. Allergy **9**:555, 1938.

35. Harkavy, J.: Hypersensitiveness to Tobacco and Biopsy Studies of Skin Reactions in Vascular Disease, J. Allergy **9**:475 (July) 1938.

36. Boyd, A. M.: Thromboangiitis Obliterans: A Clinical Study, St. Barth. Hosp. Rep. **71**:151, 1938.

and not as a consequence of intimal disease. Inflammatory or degenerative change in the vessel wall was conspicuous by its absence. In the distal type the initial symptoms were confined to the toes, usually coldness, numbness, ulceration or gangrene. In many cases the symptoms simulated orthopedic disturbances of the feet. The larger vessels were found to be patent, and postural color changes were usually limited to the affected toes. Focal sepsis in the nose or throat was a common finding. Arteriographic examination showed occlusion of the plantar arteries, which were replaced by tortuous collateral channels. Histologically, the lumen was reduced in size as a result of intimal proliferation, although the remainder of the lumen was usually blocked by clot. Fibroses were present in the media. There was no perivascular cuffing of the small vessels in the adventitia. The author was unable to reach definite conclusions as to the etiologic aspects but was impressed with the presence of focal infection in most of the cases of the distal type.

Horton [37] reported a statistical study of 948 patients suffering from thromboangiitis obliterans. These patients came from every state in the union, except three, and from ten foreign countries. More than twenty-eight different nationalities were represented; 28 per cent of the subjects were Jews. The same fundamental pathologic process was present in all, and the signs and symptoms, as well as the clinical course of the disease, were strikingly similar in all. Ninety-eight per cent of the patients were men. Twenty-one of the patients were women. The mean age of the men was 41.8 years and of the women 38.8 years. Tobacco was used by 93 per cent of the patients. Amputation was undergone by 401 of the 948 patients. Of the Jewish patients, 33.6 per cent underwent amputation, compared with 45.6 per cent of those of other national or racial groups. A study of the cases in which amputation was done for three, five and ten year periods after the onset of the disease indicated that approximately 70 per cent of the patients will go for a period of three years from the onset without the necessity of amputation, whereas only 60 per cent will go for a period of five years and only 40 per cent for a period of ten years.

Of the 175 patients with thromboangiitis obliterans known to be dead, 5 were women. It was interesting to note that coronary heart disease ranked first as the cause of death, 47 having died of it; 12 patients died of cerebral hemorrhage, 12 with gangrene or following amputation, and 7 of fatal pulmonary embolism. The others died of known but unrelated causes. Horton expressed the belief that early diagnosis and thorough education of the patient concerning the nature of his disease and the care of his extremities made for a better outlook.

37. Horton, B. T.: The Outlook in Thromboangiitis Obliterans, J. A. M. A. **111**:2184 (Dec. 10) 1938.

From the same clinic, Fatheree and Hines [38] reported on 22 patients with thromboangiitis obliterans who died, including 9 on whom necropsy was performed. In 16, or 72 per cent of the group, extraperipheral vascular lesions played a dominant role as the cause of death. As in Horton's group, coronary thrombosis was the most common lesion producing death. The average age at death was 41 years. In none of the patients on whom postmortem examination was made were lesions of the visceral arteries found which were typical of those described by Buerger.

In a histopathologic study of the peripheral nerves in a series of 20 cases of thromboangiitis obliterans, Barker [39] noted various combinations of wallerian degeneration, fibrosis, edema, atrophy, lymphocytic infiltration, inflammation and thrombosis of the vasa vasorum in all but 1 case. Definite correlation was found between wallerian degeneration and the clinical syndrome of ischemic neuritis. In 2 cases in which section of the nerves failed to relieve pain, it was believed that the ischemic inflammatory and degenerative lesions of the nerves had already occurred at levels proximal to the site of section.

Roth, Maclay and Allen [40] studied the blood of 105 patients with thromboangiitis obliterans. The values for serum calcium, serum protein, blood urea, serum lecithin and serum phosphorus were found to be within normal limits. In most instances the blood volume, the hematocrit value and the concentration of fatty acids and of cholesterol in the plasma were found to be normal. In some instances, however, the blood volume was slightly decreased, and the concentration of fatty acids in the plasma and that of cholesterol were slightly increased. The stage of the disease process was not mentioned. Theis and Freeland [41] studied the venous blood of the involved extremity in 7 patients with acute thromboangiitis obliterans. They found increased blood viscosity, rapid sedimentation of the cells, rapid coagulation, greatly increased alkalinity, low or normal cell counts and oxygen saturation of arterial blood and a low carbon dioxide content of the blood. These conditions, however, were not noted in 21 clinically improved or recovered patients. Oxygen saturation of the venous blood appeared to follow clinical improvement, being normal when there was freedom from pain

38. Fatheree, T. J., and Hines, E. A., Jr.: Fatal Complications of Thromboangiitis Obliterans: A Clinical Study, Proc. Staff Meet., Mayo Clin. **13**:342, 1938.

39. Barker, N. W.: Lesions of Peripheral Nerves in Thromboangiitis Obliterans, Arch. Int. Med. **62**:271 (Aug.) 1938.

40. Roth, G. M.; Maclay, E. V., and Allen, E. V.: Blood in Thromboangiitis Obliterans, Arch. Int. Med. **62**:413 (Sept.) 1938.

41. Theis, F. V., and Freeland, M. R.: The Blood in Thromboangiitis Obliterans, Arch. Surg. **38**:191 (Feb.) 1939.

at rest only to return to a high level with recurrence of the disease. This suggested to the authors that a disturbance in the utilization of oxygen is one of the conditions in the complex physiology of the blood and tissue metabolism which are responsible for the acute symptoms. Unlike Roth, Maclay and Allen, they were able to confirm the results of other authors in noting disturbances in phospholipin and cholesterol metabolism. Low basal metabolic rates were noted in all.

They also investigated in 6 cases the etiologic role of typhus fever in thromboangiitis obliterans. All of the cutaneous tests with antigen supplied by Goodman were negative.

Hausner and Allen [42] concluded from a study of reports of 23 cases of thromboangiitis obliterans collected from the literature, in which there occurred both cerebral and peripheral involvement, that lesions of the cerebral vessels, while not always characteristic of thromboangiitis obliterans, may be present in persons with this disease of the extremities who do not have syphilis, hypertension, diabetes or other detectable causes for cerebrovascular lesions. They have observed 11 patients with thromboangiitis obliterans involving the extremities in whom there was evidence of vascular lesions involving the brain. These were encountered in a study of 500 patients with peripheral involvement. The duration of the peripheral disease in this group varied from five months to twenty years. The ages of the patients varied from 35 to 59 years. In most of the patients the cerebral complications occurred following the onset of the peripheral disease. The cerebral lesions preceded the peripheral symptoms in only 3 patients. In these 3 hemiplegia was present one, two and fourteen years, respectively, before the onset of the peripheral symptoms. Thromboangiitis obliterans must therefore be suspected in cases of cerebrovascular disease of obscure cause. The main neurologic symptom was hemiplegia, which occurred transiently once, several times or permanently. Some patients showed confusion, disorientation, aphasia and loss of memory, symptoms which frequently cleared up entirely. Hemianopia, present in 2 patients, disappeared in 1 patient following sympathectomy. The symptoms depended chiefly on the location of the cerebral lesion. This complication may be noted more frequently if attention is directed to it. This study emphasized that cerebrovascular complications may occur in cases of thromboangiitis obliterans and may precede evidence of thromboangiitis obliterans of the extremities. It is also apparent that peripheral thromboangiitis obliterans may be the least serious part of a disease which may be disabling and in which life may be terminated by cerebral or cardiac involvement.

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42. Hausner, E., and Allen, E. V.: Cerebrovascular Complications in Thromboangiitis Obliterans, Ann. Int. Med. **12**:845, 1938.

Cases in which thromboangiitis obliterans was associated with diabetes were reported by Collens and Wilensky (1 case) [43] and Helm and Horton (1 case).[44] The former authors resorted to biopsy to establish the diagnosis. Cases of thromboangiitis obliterans in women were reported by Millman [45] and Robinson.[46] The authenticity of Robinson's case is doubtful from the evidence supplied. The condition was associated with the menopausal syndrome.

ARTERIOSCLEROSIS

New concepts of the biologic aspects of arteriosclerosis were published in an excellent book by Winternitz, Thomas and LeCompte.[47] The assumption which guided these studies was that blood extravasating within the wall, especially the intima, of the aorta and large arteries may be at least one source of the lipoidal deposit and the cause of the formation of the atheromatous plaque which characterizes human intimal arteriosclerosis. This assumption was based on the knowledge that lipoidal deposits at other sites may have their origin in extravasated blood and on the frequent observation of vascularization and hemorrhage within the lesions of human simple intimal arteriosclerosis. It was recognized by the authors that the mere demonstration of blood vessels and of extravasated blood in arteriosclerotic plaques does not constitute proof of a primary causal relationship between the former and the latter. The reverse may be true, for the vascularization and hemorrhage could be, as most students of the subject have thought, secondary to the lipoidal deposit. The authors' view has found support in their convincing demonstration by special technical methods of an "extensive vascular network" in the intima of normal blood vessels of a number of animal species other than man. The origin of the anastomosing intimal vasa has been demonstrated to be from (1) the adventitia, (2) the region of orifices of branches and (3) the lumen of the vessel. Two outstanding weaknesses must be explained before the significance of these studies can be fully recognized and the results applied to the problem of the origin of simple arteriosclerosis in man. The first difficulty is that, while the demonstration of anastomosing channels in

43. Collens, W. S., and Wilensky, N. D.: Thromboangiitis Obliterans in a Diabetic, Am. Heart J. **17**:624 (May) 1939.

44. Helm, S., and Horton, B. T.: Thromboangiitis Obliterans Associated with Diabetes Mellitus, Ann. Int. Med. **12**:1493 (March) 1939.

45. Millman, S.: Thromboangiitis Obliterans in Woman: Report of a Case, Am. Heart J. **15**:746 (June) 1938.

46. Robinson, S. K.: Thromboangiitis Obliterans in a Woman with the Menopausal Syndrome, M. Rec. **149**:233, 1939.

47. Winternitz, M. C.; Thomas, R. M., and LeCompte, P. M.: The Biology of Arteriosclerosis, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

the intima of normal arteries of different animal species can be accepted, it is a fact that the arteriosclerosis which occurs in such animals is most commonly medial, characterized by degeneration and calcification of this coat and not by atheromatosis, which is an important part of the lesion of simple intimal arteriosclerosis in man. The second difficulty is that these authors have failed to demonstrate anastomosing channels in the intima of the normal human aorta and arteries; yet it is in this very location that simple arteriosclerosis develops in man. Until these obstacles are successfully overcome there can be no strict application of the results of this work to the complex problem of the genesis of human arteriosclerosis.

Leary [48] questioned the etiologic role of intimal hemorrhage in arteriosclerosis. It was his opinion that the normal intima was not vascularized and that vascularization occurred only in connection with vascular lesions in which repair had taken place. He reasoned that since the vessels arose only as a result of a repair process and since the lesions were of the advanced atherosclerotic type the hemorrhages from such vessels must be a late phenomenon and therefore not of etiologic importance. He expressed the belief that the cholesterol found in atherosclerotic lesions was not a deposit from the blood of these hemorrhages, because of the minute amounts of this material in the original hemorrhage. He offered the opinion that the cholesterol was most likely transported to the site in macrophages or as free or ester cholesterol in the blood.

Hines [49] made a clinical study of 280 patients with thromboarteriosclerosis obliterans. The ratio of males to females was found to be 6 to 1. The age range was from 35 to 94, 70 per cent of the patients being in the fifth, sixth and seventh decades of life. No significant difference in racial incidence was noted. In only 3 patients was either the radial or the ulnar artery occluded. This was considered an important finding because of the contrast with thromboangiitis obliterans, in which involvement of the vessels of the upper extremities is not uncommon. No correlation could be made between the extent of calcification shown by roentgenograms and thrombosis with occlusion, although the incidence of calcification among men was 69 per cent and among women 31 per cent. Diabetes was present in 20.3 per cent of the patients. In this group the incidence of ulcer and gangrene was greater than in the nondiabetic group. Ischemic neuritis was noted in 8

48. Leary, T.: Vascularization of Atherosclerotic Lesions, Am. Heart J. **16**:549, 1938.

49. Hines, E. A., Jr.: Thromboarteriosclerosis Obliterans: A Clinical Study of Two Hundred and Eighty Cases, Proc. Staff Meet., Mayo Clin. **13**:694 (Nov. 2) 1938.

per cent and paresthesias in 5 per cent. Hypertension was noted in 35 per cent. However, this figure was considered low, because many had a latent form of hypertension, as demonstrated by changes in retinal arteries and by cold pressor tests. Of the 116 patients about whom there was satisfactory follow-up information, 54.6 per cent died within three years after their first admission. The majority died in a manner suggestive of coronary thrombosis. The incidence of deaths was not appreciably higher in the group of patients who had diabetes. The incidence of amputation was found to be 25 per cent, a figure considered low because of a presumed additional 5 per cent who might have had amputation elsewhere.

Kramer [50] studied the peripheral circulation in 100 diabetic persons selected at random. Taking the group as a whole, he found the incidence of sclerosis to be 38 per cent. However, there was a marked increase in the incidence with each decade. Hypertension was present in 28 per cent of those showing evidence of sclerosis. Hyperglycemia did not appear to influence the development of sclerosis. Elevated levels of blood cholesterol were found for only 23 per cent of all the diabetic patients and only 21 per cent of the arteriosclerotic ones had elevated lipid readings. Roentgen studies of the lower extremities revealed calcium in the walls of blood vessels in 63 per cent of the patients in the arteriosclerotic group. Fourteen patients showing no evidence of sclerosis as demonstrated by this method had other indications of vascular damage. All the patients in the arteriosclerotic group showing normal responses in histamine tests excepting 2 had correspondingly good oscillometric readings. Sixty-seven per cent showed normal responses to histamine. Kramer expressed the opinion that many methods of study were necessary to diagnose arteriosclerosis. The results of histamine studies were a most reliable guide to presence or absence of sufficient collateral circulation. The number of patients having poor or no pulsations of the peripheral vessels of the lower extremities compared favorably with the number showing a poor oscillometric index. The ophthalmologic examination of the fundi, the roentgen study of the lower extremities and the blood pressure readings demonstrated a relatively equal incidence of arteriosclerosis.

Stroud and Shumway [51] noted the occurrence of intermittent claudication in a certain number of persons subject to coronary occlusion. In a series of 57 patients with coronary occlusion 7 had inter-

50. Kramer, L. I.: Various Methods of Determining the Early Diagnosis of Arteriosclerosis in Diabetes, New England J. Med. **220**:278 (Feb. 16) 1939.

51. Stroud, W. D., and Shumway, N. P.: Intermittent Claudication as an Early Symptom of Cardiovascular Disease, Pennsylvania M. J. **41**:894, 1938.

mittent claudication, as compared with 1 in a series of 106 patients without heart disease. They also noted that patients with hypertension were more likely to complain of cramps in their legs at night than normal persons.

Randall [52] studied the lipid composition of nerves from arteriosclerotic and diabebtic subjects. The peripheral nerves from these subjects showed marked decreases in phospholipids, cholesterol and cerebrosides and an increase in neutral fat but no significant change in water content. The posterior tibial nerve showed more extensive change from normal than the sciatic and the latter more than the femoral. The femoral, sciatic and posterior tibial nerves from normal subjects did not show significant differences in composition. The greater extent of chemical change in the more distal parts of the nerves was indicative of an inadequate blood supply and concomitant anoxemia resulting in decomposition of the lipid constituents.

Millet [53] described 2 fatal cases of diabetic gangrene of the face. In both cases the lesions in their early stages resembled erysipelas, with later a breakdown of tissue.

PERIARTERITIS NODOSA

Articles on this subject consist mainly of case reports, each bearing on some etiologic phase of the disease. Berger and Weitz [54] reported a case in which periarteritis nodosa developed in an allergic person while this person was under observation. An antemortem diagnosis was made on the results of a biopsy of muscle. The authors believed that this case substantiated the theory of the allergic background of this disease. Becker [55] reported the case of a boy of 13 admitted with a tonsillar abscess in whom later cardiac insufficiency developed with fatal termination. Autopsy confirmed the diagnosis. Cleland [56] observed periarteritis nodosa in 3 of 4,000 autopsies. In 1 of these cases rheumatic vegetations were present on the mitral valve. He stated the opinion that there was a definite relation between periarteritis nodosa and rheumatic fever and that it was possible that the former disease was in some cases an allergic response to the agent

52. Randall, L. O.: Changes in Lipid Composition of Nerves from Arteriosclerotic and Diabetic Subjects, J. Biol. Chem. **125**:723 (Oct.) 1938.

53. Millet, J.: Diabetic Gangrene of the Face, J. A. M. A. **112**:1143 (March 25) 1939.

54. Berger, S. S., and Weitz, M. A.: Periarteritis Nodosa, J. Allergy **9**: 489 (Aug.) 1938.

55. Becker, W.: Ueber Periarteritis nodosa, Med. Klin. **34**:869, 1938.

56. Cleland, J. B.: Periarteritis Nodosa: Report of Two New Cases, M. J. Australia **1**:847, 1938.

of rheumatic fever. Matras [57] described a case in which periarteritis nodosa occurring in the vessels of the skin was associated with extensive hemorrhages and gangrene.

THROMBOSIS

LeFevre [58] reported the case of a boy of 16 in whom thrombosis of the right posterior tibial artery developed following a simple contusion inflicted by a golf ball. Symptomatic and objective improvement followed the administration of passive vascular exercise. Adson and Allen [59] reported thrombosis of the arteries of the right upper extremity secondary to the presence of an anomalous first rib. Watkins [60] reported gangrene of various digits in both upper and lower extremities of an infant 11 weeks old. He held, because of the sequence of events leading to the gangrene, that the condition was most likely arteritis secondary to recent streptococcic infection producing thrombosis of the phalangeal arteries. An embolic phenomenon seemed unlikely because of the nature of the infant's illness.

RAYNAUD'S DISEASE

Lewis [61] compared the pathologic changes in the arteries of the fingers in warm-handed people with those in patients with so-called Raynaud's disease. The warm-handed adults, used as controls, usually showed distinct intimal thickening in the digital arteries increasing with age. General thickening was the rule after the age of 50. The thickening consisted of hyperplasia of the intimal tissues. After 60 years the thickening was conspicuous. In digital arteries subject to intermittent spasm of the type exemplified in the mildest form of so-called Raynaud's disease there was no more intimal thickening than was to be found in the arteries of warm-handed people of similar age. In digital arteries of the same type but with spasm of greater severity more intimal thickening than usual was found, but it was not more than that found in many subjects presenting no symptoms. Attacks of discoloration of the fingers in these cases were ascribed to

57. Matras, A.: Zur kutanen Form der Periarteriitis nodosa, Wien. klin. Wchnschr. **51**:991 (Sept. 16) 1938.

58. LeFevre, F. A.: Arterial Thrombosis Following Simple Contusion, Am. Heart J. **17**:111 (Jan.) 1939.

59. Adson, A. W., and Allen, E. V.: Vascular Clinics: VI. Thrombosis of Arteries of the Right Upper Extremity Resulting from Anomalous First Rib, Proc. Staff Meet., Mayo Clin. **13**:637 (Oct. 5) 1938.

60. Watkins, A. G.: Gangrene of the Extremities in an Infant, Arch. Dis. Childhood **13**:366, 1938.

61. Lewis, T.: The Pathological Changes in the Arteries Sypplying the Fingers in Warm-Handed People and in Cases of So-Called Raynaud's Disease, Clin. Sc. **3**:287, 1938.

overaction of the muscular wall. Hyperplasia of the media was not found in any of them; the digital arteries were normally very muscular. In 2 cases of intermittent spasm in which the finger tips presented the scars of small healed necroses, obstructive disease of the digital arteries was discovered. The arterial wall generally presented intimal hyperplasia, the lumens being conspicuously reduced or actually occluded by new cellular tissue or by recent or organized thrombus. The conspicuous lesions were present in scarred and unscarred fingers. In cases of intermittent spasm in which the fingers presented unhealed necroses, thrombotic obstruction of the digital arteries was the rule. The thrombi were seen in various stages of organization. In cases of bilateral discoloration and necrosis of fingers, in which there had been no previous attacks of discoloration, the predominant lesion was thrombosis, and the thrombi were in various stages of organization. Similar lesions were found in necrosed and nonnecrosed fingers in these cases. Lewis suggested that in many patients experiencing attacks of discoloration leading to necrosis of the fingers, symptoms were determined by an initial thrombosis. He was not able to present evidence that attacks of digital arterial spasm produced thickening of the medial or intimal coats of the digital arteries; he thought, however, that it might lead to thrombosis. In patients with diffuse scleroderma presenting attacks of discoloration of the fingers there was an occlusive disease of the digital arteries. In the intimal thickening, hyperplasia of the original tissues and connective tissue growth play conspicuous parts. Organizing thrombi may be found in the lumen. He expressed the belief that in the presence of a full radial pulse failure to elicit any capillary pulsation at the tips of the fingers by adequately heating the hand indicated a considerable reduction or obliteration of the lumens of digital arteries by structural disease. The same author [62] studied 6 cases of Raynaud's disease shortly after preganglionic sympathectomy. Discoloration of the fingers occurred spontaneously or was induced within a few days after the operation in 3 cases. In 2 of the remaining 3 cases abnormal reactions to cold were produced with difficulty before operation, but easily after the operation. He expressed the belief that preganglionic sympathectomy did not bring the fingers to a normal state, as a local abnormality remained which could be displayed in a measure related to the abnormality displayed before operation. He offered the opinion that the attacks in Raynaud's disease were due not to excessive action of the vasomotor system but to a local fault and that in some cases this was an occlusive structural disease, as mentioned. There appears to be an

62. Lewis, T.: Raynaud's Disease and Preganglionic Sympathectomy, Clin. Sc. **3**:321, 1938.

increased susceptibility of the vessels to cold. He showed that full vasodilatation declined slowly during a period of a week after operation. Houston and Johnson [63] reported the case of a young woman suffering from Raynaud's disease who had calcified nodules in the soft tissue of her fingers.

ANGIOSPASTIC DISTURBANCES

Gifford and Marquardt [64] described a type of central retinopathy affecting young or middle-aged persons with little or no increase in general blood pressure. In all of the patients examination revealed definite signs of peripheral vascular spasm. The authors concluded that the ocular symptoms were purely angiospastic, on the following grounds: A high degree of arterial spasm was found elsewhere, the attacks of blindness were transient, these attacks were frequent with definite ophthalomoscopic findings; and antispasmodic treatment resulted in complete or almost complete recovery of function. The treatment consisted in administration of antispasmodic drugs, as the nitrites, of typhoid vaccine or of tissue extract, along with avoidance of tobacco, exposure to cold and psychic trauma. Perry and Davie [65] reported symmetric peripheral gangrene of the lower limbs developing shortly before death in a person with congestive heart failure as a result of hypertensive heart disease. They discussed the possibility that this rare occurrence was due to reflex vasoconstriction leading to redistribution of the circulating blood in an attempt to protect the vital organs from the effects of a diminished cardiac output. At autopsy the aorta presented a moderate degree of atheroma, but the iliac, femoral and popliteal arteries showed no obstruction on either side. Warembourg, Linquette and Ravaut [66] noted that arteriolar spasm occurred frequently in patients with cardiac insufficiency. Various tests were made on 64 patients with heart disease to demonstrate this phenomenon. The relationship between angiospastic conditions and hypocalcemia was again discussed by Norman.[67] Cases in which migraine was associated with various peripheral vasospastic phenomena, such as blanching or paresthesias of the fingers, were discussed. He held that these headaches were thus angiospastic in nature. A large number of the patients

63. Houston, C. J., and Johnson, E.: A Case of Unusual Calcium Deposition Due to Raynaud's Disease, Canad. M. A. J. **39**:60, 1938.

64. Gifford, S. R., and Marquardt, G.: Central Angiospastic Retinopathy, Arch. Ophth. **21**:211 (Feb.) 1939.

65. Perry, C. B., and Davie, T. B.: Symmetrical Peripheral Gangrene in Cardiac Failure, Brit. M. J. **1**:15 (Jan. 7) 1939.

66. Warembourg, H.; Linquette, M., and Ravaut, J.: Arteriolar Spasm in Cardiac Insufficiency: Its Therapeutic Consequences, Presse méd. **46**:1761, 1938.

67. Norman, G. F.: Blood Calcium: Its Relation to Certain So-Called Angiospastic Conditions, West. J. Surg. **46**:513 (Oct.) 1938.

were relieved by no other therapy than that of giving viosterol to raise the blood calcium.

CIRCULATION AND ARTHRITIS

Kling [68] studied the joints and vessels of the lower extremities of patients who had undergone amputation for gangrene. The group included 3 patients with thromboangiitis obliterans and 10 with arteriosclerosis. In both types of patients the vessels of the extremities showed advanced lesions. In those with thromboangiitis obliterans the synovial vessels were found to be frequently involved with no hypertrophy of the synovial membrane. In those with arteriosclerosis, however, the vessels of the synovia were normal or moderately affected and in only 2 were the membranes definitely hypertrophied. Subacute synovitis of the ankle and knee joints was present in a patient with thromboangiitis obliterans, and in another venous congestion of the membrane was noted. Pronounced osteoarthritis was present in only 2 of the patients with arteriosclerosis. In all patients past 40 years of age slight erosion of the articular cartilage was noted, which corresponded to that found in a control group of similar age. The author was thus unable to substantiate the vascular theory of osteoarthritis.

ARTERIOVENOUS ANEURYSMS

Reid and McGuire [69] presented another series of 30 aneurysms, of which 21 were arteriovenous and 9 cirsoid. Clinical observations, surgical procedures and experimental studies on dogs were presented. No aneurysm in the entire series proved fatal. There were 8 arteriovenous aneurysms which had caused definite cardiac damage; with 2 there was severe cardiac decompensation. Of the 9 cirsoid aneurysms, 2 were associated with evidences of some cardiac damage. In every instance in which the heart was demonstrably affected, closure or excision of the fistula was followed by cardiac improvement. In the walls of the artery and vein opposite the fistula extensive calcification was noted. In 11 cases definite enlargement and thinning of the wall of the proximal artery were noted. In many cases the wall of the involved vein was definitely hypertrophied. There was no positive evidence that the circulation time was definitely affected by the fistula. The authors' studies failed to confirm the observations of Holman and others who reported a large increase in blood volume in the presence of arteriovenous aneurysm. Slowing of the pulse rate when the fistula was closed was observed in 10 cases as well as in experiments on ani-

68. Kling, D. H.: The Significance of Peripheral Circulatory Disturbances for the Development of Osteo-Arthritis, Am. J. M. Sc. **197**:358 (March) 1939.

69. Reid, M. R., and McGuire, J.: Arteriovenous Aneurysms, Ann. Surg. **108**:643 (Oct.) 1938.

mals. The extent of this slowing of pulse rate varied greatly and seemed to be directly related to the seriousness of the cardiac damage and the size of the fistula. Venous pressures appeared to be unaffected by arteriovenous aneurysms unless there was some evidence of cardiac decompensation, at which time the changes in venous pressures were similar to those which normally occur in cardiac decompensation. A rise in both systolic and diastolic pressure following closure of arteriovenous fistula was observed in 13 cases. An extensive collateral circulation around an arteriovenous fistula was demonstrated in 6 instances. This extensive collateral circulation makes the occurrence of gangrene after excision of chronic arteriovenous fistula practically unknown. The circulation distal to the fistula may be impaired, as evidenced by absence of pulses, coldness of the part, cyanosis and occasional chronic ulcers. Nerve paralyses associated with the arteriovenous condition occurred in 4 cases. Intracranial arteriovenous aneurysms developed in 3 cases, pulsating exophthalmos in 2 and a fistula between the ophthalmic vessels behind the eyeball in 1.

ERYTHROMELALGIA

Smith and Allen [70] held that "erythermalgia" was a more descriptive term than "erythromelalgia" for the syndrome of heat, redness and pain of an extremity. The latter, they said, was not entirely adequate because it did not denote the importance of heat. The rather definite clinical picture was described by the authors as a syndrome affecting one or more extremities and consisting of discoloration and distress, both of which were dependent entirely on the temperature of the skin, an increase of which constituted the third component. The condition might occur as a primary disturbance, or it might be secondary to such a condition as polycythemia vera. The diagnosis depended on the establishment of a close relationship between the occurrence of the distress and the temperature of the skin. When the temperature of the skin increased above a critical point, usually 32 C., the distress occurred, and when it decreased below this point the distress disappeared. They believed that the distress itself resulted from a susceptibility of the skin to increased temperatures, a condition which did not occur in normal persons.

A case of erythromelalgia associated with chronic gout was described by Markel.[71] Relief was obtained for two years by an intravenous injection of typhoid vaccine.

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70. Smith, L. A., and Allen, E. V.: Erythermalgia (Erythromelalgia) of the Extremities, Am. Heart J. **16**:175, 1938.

71. Markel, J.: Erythromelalgia: Report of Case of Its Association with Chronic Gout with Relief of Symptoms for Two Years After Intravenous Administration of Typhoid Vaccine, Arch. Dermat. & Syph. **38**:73 (July) 1938.

ACROCYANOSIS

Day and Klingman [72] reported a study of the effect of sleep on the cutaneous temperature of a 6½ year old girl with acrocyanosis. During sleep there was spontaneous warming and reddening of the hands and feet. Under these conditions the hands responded in a parallel way with the rest of the body to warm and cold foot baths. Local cooling of the hand under induced sleep did not cause vasoconstriction. The authors expressed the belief that their studies supported the theory of a central rather than a local origin of this abnormal vasomotor tone. Microscopic studies of the capillaries at the nail base showed sluggish blood flow and venous dilatation.

GLOMUS TUMOR

Grauer and Burt [73] reported 2 cases of glomus tumor located on the penis. This report was of interest not only because of the unusual site but because in 1 case the onset occurred at 1 year of age.

Doane [74] reported an additional case of a glomus tumor on the finger of a 31 year old woman.

PHLEBITIS AND THROMBOSIS

Many articles have been published on this subject during the current year. Few new ideas have been presented. Arterial symptoms secondary to phlebitis of the extremities were discussed by many authors (Uggeri and Massone [75]; Audier and Haimovici [76]; Gregoire [77]; Zehnder [78]; Ochsner and DeBakey [79]). Uggeri and Massone [75] expressed the opinion that ischemia might be caused by one of three conditions, namely, arteritis from dissemination of phlebitis, secondary arterial spasm or a combination of both. Audier and Haimovici [76]

72. Day, R., and Klingman, W. O.: The Effect of Sleep on Skin Temperature Reactions in a Case of Acrocyanosis, J. Clin. Investigation **18**:271 (May) 1939.

73. Grauer, R. C., and Burt, J. C.: Unusual Location of Glomus Tumor, J. A. M. A. **112**:1806 (May) 1939.

74. Doane, C. P.: Glomus Tumor (Glomangioma), J. A. M. A. **112**:1049 (March 18) 1939.

75. Uggeri, C., and Massone, A.: Arterial Symptoms from Phlebitis of Limbs, Arch. ital. di chir. **49**:429 (Sept.) 1938.

76. Audier, M., and Haimovici, H.: Les gangrènes des membres d' origine veineuse, Presse méd. **46**:1403, 1938.

77. Gregoire, R.: La phlébite bleue (phlegmatia cærulea dolens), Presse méd. **46**:1313, 1938.

78. Zehnder, M.: Die Claudicatio venosa der oberen Extremitäten als Symptom, Arch. f. klin. Chir. **192**:354, 1938.

79. Ochsner, A., and DeBakey, M.: Treatment of Thrombophlebitis by Novocain Block of Sympathetics, Surgery **5**:491, 1939.

discussed venous gangrene, citing many cases reported elsewhere. In each case autopsy demonstrated an intact arterial system. Although the most logical cause appeared to be secondary arterial spasm, other possibilities were discussed. They offered the opinion that such gangrene could develop from mechanical blockage due to complete obliteration of all the veins or from stasis in terminal capillary beds resulting from a disease process in the venous loops. At autopsy no definite occlusion could be demonstrated as a direct cause for the gangrene. Gregoire [77] discussed a definite type of superficial phlebitis which was characterized by an excessive amount of vasospasm.

Zehnder [78] studied 8 cases of venous claudication in the upper extremities, resulting from strain, by means of venograms and infrared photographs. He was unable to demonstrate venous thrombosis in all of the cases. He showed that the symptoms could be produced by vasomotor changes, muscle swelling or muscle contraction. Roelsen [80] reported 7 cases of traumatic thrombosis of the axillary-subclavian vein. The condition was characterized by acute venous stasis, in part recurrent, manifested by marked venous dilatation and diffuse swelling of the upper extremity. A case of traumatic thrombosis of the deep palmar vein was reported by Snyder and Snyder.[81]

The relationship between serum sodium chloride and venous thrombosis was studied by Russo.[82] In 44 cases of thrombosis he found the sodium chloride content of the serum to be within normal limits; thus he rejects the suggestions of other authors that chloride deficiency is a cause of spontaneous thrombosis. A review of cases of hypochloremia and of experiments on animals in this connection failed to disclose a tendency toward thrombosis. The author expressed the opinion that dehydration resulting from withdrawal of sodium chloride is a problem that concerns not the blood vessels but the tissues. Consequently it has no accelerating effect on blood coagulation and is not a factor in the genesis of venous thrombosis. Moreover, the sodium chloride content of the blood has little influence on the viscosity of the blood. The author expressed the belief that venous thrombosis in patients with heart disease is not connected with dehydration procedures. According to Dougal,[83] trauma of tissue and sepsis are the two primary causative

80. Roelsen, E.: So-Called Traumatic Thrombosis of Axillary-Subclavian Veins, Hospitalstid. **81**:889 (Sept.) 1938.

81. Snyder, M. H., and Snyder, W. H., Jr.: Traumatic Thrombosis of Deep Palmar Vein, J. A. M. A. **111**:2007 (Nov. 26) 1938.

82. Russo, G.: Sodium Chloride Content of Serum and Changes in Blood During Venous Thrombosis, Med. Klin. **35**:233 (Feb.) 1939.

83. Dougal, D.: Ætiology of Thrombosis and Embolism, J. Obst. & Gynaec. Brit. Emp. **45**:405 (June) 1938.

factors in thrombosis and embolism. Slowing of the circulation, in his opinion, is the most important predisposing cause, as thrombosis rarely occurs if the blood flows freely.

Veal,[84] since his recent publication of venographic observations in 20 cases of swelling of the arm following radical removal of the breast, has observed 26 additional cases, a total of 46 cases of swelling following operation. Twenty-two patients who did not experience swelling of the arm after such operation were studied in order to determine the possible extent of the venous obstruction existing before edema occurred. Venographic studies supplemented with determinations of venous pressure proved valuable as a means of differentiating between the several forms of arm swelling following radical amputation of the breast. Simple lymphatic edema was the least frequent cause of swelling of the arm after such an amputation. He believed that this form of edema might result from recurrent lymphangitis, cellulitis or cutaneous metastases. The deep veins of the arm were not primarily involved and remained patent. Edema resulting from obstruction of the axillary-subclavian vein was by far the most common cause of swelling of the arm following operation. The most frequent cause of the venous obstruction was a recurrence of the malignant growth along the course of the veins. In some cases the venous occlusion resulted from benign scar formation. In others the axillary part of the vein was occluded by the sharp angulation of its course when the arm was dependent, because of the fixation of the floor of the axilla. The venous obstruction produced a local increase in the venous pressure, and fluid escaped into the tissues. Lympathic stasis was a secondary result of the venous obstruction and if prolonged led to permanent blockage of the lymphatic flow. Infection was prone to develop, and when it did led to further obstruction and caused a greater degree of swelling. The skin then became thickened, presenting the typical picture of lymphatic edema.

Monteiro[85] described his technic for making lymphangiograms on various animals, using thorium dioxide as a contrast medium. The technic was much like that used in the injection of the lymphatics in cadavers. He demonstrated in animals that sympathectomies favor, as in the case of arteries, the reestablishment of the lymphatic circulation after the interruption of the large trunks by the development of a large number of derivative passages.

84. Veal, J. R.: Pathologic Basis for Swelling of the Arm Following Radical Amputation of the Breast, Surg., Gynec. & Obst. **67**:705 (Dec.) 1938.

85. Monteiro, H.: Lymphangiography in the Living: Method, Results and Applications, Bruxelles-méd. **19**:205 (Dec.) 1938.

TREATMENT

The present day therapy of peripheral vascular diseases is not yet entirely satsifactory. This is evident in the multiplicity of procedures, drugs and mechanical devices now used and in the fact that many such procedures have fallen into disrepute after a relatively short use.

Wollaeger, Allen and Ghormley [86] stressed the importance of persistent treatment of patients suffering from thromboangiitis obliterans, using 2 illustrative cases. In both cases major amputation was rejected in favor of conservative management. Although the patients were submitted to months of persistent medical management the end results were so satisfactory that the authors felt justified. Better and adequate conservative treatment, with less haste to amputate, was shown to be very desirable in many cases.

Wolffe [87] reported beneficial results in 60 patients with diabetic and 40 with nondiabetic arteriosclerotic gangrene from the use of pancreatic (enzyme free) tissue extract. Complete healing was obtained in 75 per cent of the patients. Injections were repeated whenever there was a complaint of pains or cramps in the legs and difficulty in walking. Many of his patients had been under observation for years. To many of them additional remedies were given simultaneously, such as papaverine hydrochloride, heat, diets low in cholesterol, insulin when needed, and alcohol. He stated that pancreatic extract seemed not only to produce an early arrest of pathologic processes but also to stimulate more rapid and more complete repair than other conservative means.

The treatment of erythromelalgia (or erythermalgia) was not found to be uniformly successful by Smith and Allen.[70] They found it important to determine whether there was any condition, such as polycythemia, to which erythermalgia might be secondary. Under such a circumstance the treatment of the syndrome affecting the extremities would be the treatment of the condition which produced it. Surprisingly, in some cases acetylsalicylic acid in amounts of 10 grains (0.65 Gm.) produced marked relief, persisting for as long as several days. No adequate explanation of this was available. Some symptomatic relief could be obtained by avoiding procedures that cause vasodilatation in the extremities. Avoidance of exposure of the feet to warmth, as in riding in the front seat of an automobile, alleviated some of the distress, as well as the use of light socks or stockings and of sandals or perforated shoes. When simple measures failed, it became

86. Wollaeger, E. E.; Allen, E. V., and Ghormley, R. K.: The Value of Persistence in the Treatment of Thromboangiitis Obliterans: Report of Two Illustrative Cases, Minnesota Med. **22**:305 (May) 1939.

87. Wolffe, J. B.: Pancreatic Extract (Enzyme-Free) in the Treatment of Diabetic and Arteriosclerotic Gangrene, Am. J. Surg. **43**:109, 1939.

necessary in some cases to anesthetize the skin of the feet by section, by crushing or by injecting alcohol into such peripheral nerves as the posterior tibial, peroneal and sural. The logical procedure appeared to be to attempt to desensitize the skin to heat.

Sedwitz [88] found the paraffin boot to be a valuable adjunct in the therapy of peripheral vascular diseases. He found that it produced and maintained heat in a diseased extremity. The temperature of the skin and oscillometric readings were found to be increased as compared with those of normal persons when the boot was used prior to treatment by intermittent venous occlusion. Montgomery and Starr [89] described in detail the construction of four well known mechanical devices for use in the therapy of peripheral vascular disorders. Each had been selected because of low cost and efficiency, having been used successfully by these physicians for periods of from one to four years. These devices consist of (1) a simple thermoregulator for maintaining an optimal temperature in a foot cradle, (2) an inexpensive apparatus for giving drugs by iontophoresis, (3) a bed so constructed that the patient is able to be comfortable with the legs in a dependent position and (4) an original small suction pressure apparatus to be inserted on the fingers. With the latter apparatus, reddening of the skin in the suction phase with blanching during pressure was easily demonstrated. This was found to be useful for home treatment by persons suffering from diseases confined to the fingers.

The Council on Physical Therapy of the American Medical Association [90] accepted the Sanders vasocillator as an adjunct in the therapy of peripheral vascular diseases. The vasocillator is a bed which is capable of oscillating up and down at a regular cycle, which can be adjusted at will. It is capable of giving exercise similar to Buerger's exercise to persons unable to perform active movements. The patient learns to sleep in the bed, thus making it possible for the exercise to be continued over long periods. It was the opinion of the Council that this bed had a limited therapeutic usefulness and that no more could be expected from it than could be achieved by the conventional Buerger exercise.

Veal and McCord [91] studied the oxygen saturation of venous blood after true reactive hyperemia and after intermittent venous occlusion.

88. Sedwitz, S. H.: The Paraffin Bath in Peripheral Vascular Disease, Arch. Phys. Therapy **20**:165, 1939.

89. Montgomery, H., and Starr, I.: Four Physiotherapeutic Devices for the Treatment of Peripheral Vascular Disorders, Am. J. M. Sc. **197**:485 (April) 1939.

90. Sanders Vasocillator, Acceptable, report of the Council on Physical Therapy, J. A. M. A. **111**:2016 (Nov. 26) 1938.

91. Veal, J. R., and McCord, W. M.: Blood Oxygen Changes Following Intermittent Venous Occlusion, Am. Heart J. **17**:401 (April) 1939.

The test was conducted on 11 healthy male subjects, a blood pressure cuff being used for compression. Studies were made on the arm, blood being drawn from the antecubital veins under oil. The maintenance of complete compression over periods of five to eight minutes was followed in 9 of 11 cases by a definite rise in the oxygen saturation of the venous blood one minute after its release. In most cases the elevation was maintained at the end of three minutes. Intermittent venous occlusion, on the other hand, even in the presence of a normal circulatory system, was usually followed by a lowering of the oxygen saturation of the venous blood at the end of one and three minutes after release. In the latter experiment cuff pressures varied from 60 to 80 mm. of mercury, with a ratio of compression to release of 2:2 and 2:1. The authors assumed from these experiments that reactive hyperemia increased the blood flow and also increased the volume of the flow. Intermittent venous occlusion, on the other hand, produced no increase in rate or in volume of blood flow, but the authors could not deny the possibility of some chemical changes occurring in the tissues incidental to the venous congestion.

A similar study was made by Harpuder and Stein,[92] who studied the effect of mild hyperemia on the extremities of healthy and diseased persons. For each subject the venous compression was less than 40 mm. of mercury and lasted forty minutes, being then followed by release. Studies of oxygen, carbon dioxide, lactic acid and total oxygen capacity of venous blood were made. In healthy adults the oxygen content of the venous blood was definitely decreased, whereas in patients with occlusive vascular disease it was increased. Insignificant changes of the carbon dioxide content occurred in healthy persons; however, it was decreased in only 3 of those with diseased extremities. Oxygen capacities and lactic acid values changed very little. As these values changed slightly and returned to normal levels on release, the authors concluded that hyperemia did not occur after release of venous pressures below 40 mm. of mercury. Studies with the capillary microscope during compression showed the capillaries to dilate and increase in number, but the flow appeared to be slower. Clinically, improvement was noted in patients suffering from old indolent ulcers, but those with gangrene, cellulitis and pain at rest were only slightly improved.

Kountz [93] found the suction pressure form of therapy to be of little value in his hands. He experimented with this type of machine on the extremities of persons who had just died. Blood flow was maintained

92. Harpuder, K., and Stein, I.: Therapeutic Value of Passive Hyperemia in Peripheral Vascular Disease, Arch. Phys. Therapy **20**:9 (Jan.) 1939.

93. Kountz, W. B.: Re-Establishment of the Circulation in Extremities, Arch. Phys. Therapy **20**:157 (March) 1939.

by a profusion apparatus using especially prepared animal blood. Under these experimental conditions he noted that a continuous flow could be obtained only if the venous system was full and that such a flow was impossible when the venous system was collapsed, even though the arterial pressure was increased several times. He also noted, especially in diseased extremities, that the obstruction to the passage of blood could be relieved by perfusion of hypertonic saline solution. This he explained by the idea that the saline solution probably had a dehydrating influence on the swollen capillary endothelium. Having established maximum blood flow in his apparatus, he applied the suction pressure machine to the limb. During the negative phase of the cycle a definite decrease in the arterial inflow and venous output was noted. In the limbs of 3 persons, however, immediately after the negative phase of the cycle had begun there was a slight increase in the arterial inflow, whereas immediately after positive pressure was applied, the outflow from the venous side was increased. He devised an apparatus containing a series of blood pressure cuffs which tended to milk the blood into the leg. The highest cuff was inflated to a pressure of 40 mm. of mercury, and each distal cuff was inflated to pressures below this level. The system was inflated and deflated every six minutes. Experimentally he found this machine superior to those of the pavaex type. Heat up to 40 C. increased the flow about 8 per cent in normal extremities but very little in diseased extremities. Iontophoresis produced a similar response. The effect of this apparatus on local occlusion was studied. The increase in flow depended mainly on the location and amount of collateral circulation. Obstructions below the knee had less influence on total blood supply than those above the knee.

From these experimental studies, substantiated by clinical studies in association with Smith,[94] he believed that three principals should be observed in the therapy of occlusive arterial diseases: (1) maintenance of high venous pressure, (2) dehydration of diseased capillaries to facilitate an easy blood flow and (3) when necessary, stimulation of the heart and arterial side by hyperpyrexia or by milder means. They obtained encouraging results using the multiple cuff apparatus on 23 persons with occlusive vascular disease. This group was made up of patients with arteriosclerosis and thromboangiitis obliterans. In addition, intra-arterial injections of hypertonic saline solution were given twice weekly. Alcohol in the form of highballs was given to those with arteriosclerosis.

94. Kountz, W. B., and Smith, J. R.: Observations on Passive Vascular Exercise and Other Forms of Treatment of Peripheral Vascular Disease, Am. Heart J. **16**:55 (July) 1939.

The patients suffering from thromboangiitis obliterans received intravenous injections of typhoid vaccine. It was unfortunate from the clinical standpoint that many types of therapy were used in conjunction with one another, thus making the evaluation of each type difficult.

Paine and Levitt,[95] in a preliminary study, reported favorable results in the treatment of patients with acute and chronic thrombophlebitis by means of intermittent venous occlusion. In 11 unselected patients relief of pain, tenderness and discomfort was obtained. In some cases edema was decreased.

Barker and Counseller [96] advocated absolute rest in bed, application of moist heat and elevation for postoperative femoral and iliac thrombophlebitis. This therapy was continued for ten to eighteen days, until all evidence of active infection subsided. At this time the patient was advised to walk about with a supporting bandage, preferably of pure rubber, for as long a time as the edema persisted. In a group of 54 patients this routine was adhered to, and 77 per cent of them were able to discard the bandage within three months to a year. At that time no evidence of chronic venous insufficiency had developed. Thirteen per cent were not able to discard the bandage because of slight edema, but in none did marked edema, cellulitis or ulceration develop. In a control group of patients, after a similar length of time only 10 per cent were free from symptoms; 52 per cent presented evidence of venous insufficiency, and 38 per cent had developed severe venous insufficiency with marked swelling, cellulitis and ulceration. A postphlebitic neurosis was present in 12 per cent.

ARTERIAL HYPERTENSION

By Dr. Scupham and Dr. Van Dellen

While there have been no outstanding discoveries during the past year in regard to hypertension, the impression is gained that opinion about this disorder is crystallizing into definite form. Hypertension is no longer to be considered a disease but a symptom complex. While it must be admitted that perhaps the majority of patients with hypertension encountered fall into the group with so-called essential hypertension, each patient who presents himself with hypertension must be looked on from the point of view of etiology. The endocrine, renal and organic vascular

95. Paine, J. R., and Levitt, G.: The Treatment of Thrombophlebitis of the Deep Veins of the Lower Extremities with Intermittent Venous Occlusion, Surgery **5**:707 (May) 1939.

96. Barker, N. W., and Counseller, V. S.: Treatment of Postoperative Thrombophlebitis, Proc. Staff Meet., Mayo Clin. **13**:785 (Dec. 14) 1938.

types of hypertension are definite and distinct etiologic types. A good classification was presented by Scott:[97]

Renal	Nonrenal
1. Essential hypertension	1. Endocrine disturbances
2. Primary renal disease	(*a*) Basophilic adenoma of the pituitary
(*a*) Glomerular nephritis (acute and chronic)	(*b*) Adrenal tumor
(*b*) Pyelonephritis	(*c*) Hyperthyroidism
(*c*) Urinary obstruction	(*d*) Menopause
(*d*) Periarteritis nodosa of renal vessels	(*e*) Obesity
(*e*) Polycystic renal disease	2. Vasomotor disorders
(*f*) Severe amyloidosis of kidney	(*a*) Increased intracranial pressure
3. Coarctaction of the aorta?	(*b*) Psychic disturbances
4. Eclampsia?	(*c*) Circulatory failure
	(*d*) Complete heart block

Wright, Schneider and Ungerleider[98] called attention to a subject of which most clinicians are cognizant. There are a great deal of variation in the technic of determining blood pressure and a great deal of variation in readings due to differences in perception by persons using the same technic. This lack of uniformity in methods of observation is of great importance, and while it is obvious that personal variations cannot be controlled, it is apparent that there should be uniformity in technic at least. In the returns from a questionnaire sent to medical schools, life insurance companies and individuals, including interns, attending staff members and graduate students, extraordinary variations in technic and observation were encountered. This lack of uniformity is to be deplored, and the writers suggested that this is a subject for study by a national committee.

Scott[97] in a discussion of the renal origin of hypertension considered the evidence for and against this concept and concluded that the evidence, much of it old, all points to the view that essential hypertension is of renal origin when viewed in the light of the experimental hypertension of Goldblatt.

There can be no question in regard to the relationship of at least certain forms of hypertension to renal disease. Hypertension in association with chronic nephritis, pyelonephritis, obstruction of the lower urinary tract or polycystic kidneys is definitely accepted as being of renal origin. That in most instances so-called essential hypertension is of renal origin has been asserted by several writers and questioned by others.

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97. Scott, R. W.: Hypertension a Century After Bright, J. A. M. A. **111**: 2460 (Dec. 31) 1938.

98. Wright, T. S.; Schneider, R. F., and Ungerleider, H. E.: Factors of Error in Blood Pressure Reading, Am. Heart J. **16**:649 (Oct.) 1938.

Scott divided clinical hypertension into renal and nonrenal types. He classified primary, or essential, hypertension as a renal type. He stated further that it now appears that the clinical course pursued in hypertension is determined primarily by the vascular disease in the kidneys. The progress and extent of the vascular disease in the kidneys determine whether essential hypertension runs a benign or a malignant course. Sclerosis of the renal arteries and arterioles in his opinion leads to the renal ischemia. A humoral mechanism produces an increased muscular tone in the peripheral arterioles, which results in an increase in arterial blood pressure. The fact that many patients with hypertension have no evidence of impairment of renal function does not indicate that the hypertension is not of renal origin. He considered the hypertension associated with coarctation of the aorta as due to the ischemia which results from constriction of the aorta above the kidneys.

With this Rytand [99] was in agreement. He inferred that the increased peripheral blood pressure is on the basis of the impaired renal blood supply. This view is supported by the production of hypertension in rats by partial occlusion of the aorta proximal to at least one renal artery. Hypertension under these conditions Rytand asserted occurs only when there is living renal tissue distal to the point of partial occlusion. Occlusion after nephrectomy never results in hypertension, and hypertension disappears after nephrectomy even though the degree of mechanical obstruction is the same as that necessary to produce hypertension when renal tissue is intact.

The views of Scott are shared to some extent by Dicker,[100] who stated that diminution of the flow of blood to one or both kidneys may induce hypertension of long duration without renal insufficiency. This he also held to be of humoral origin. Thickening of the vessel walls, such as is seen in hypertension in man, he observed in dogs in which hypertension had been present for a considerable period. These animals did not show renal insufficiency. The arteriolonecrosis which occurs in malignant nephrosclerosis results in rapid development of renal insufficiency in the course of hypertension. He expressed the opinion that this process is the result of a more severe grade of vascular ischemia and at the same time results in renal insufficiency. It is primarily a vascular disease process.

Page [101] also pointed out, in discussing malignant hypertension, that the function of the kidneys may be but little impaired until late in the

99. Rytand, D. A.: The Renal Factor in Arterial Hypertension with Coarctation of the Aorta, J. Clin. Investigation **17**:391, 1938.

100. Dicker, E.: Benign and Malignant Hypertension, Bruxelles-méd. **19**: 323 (Jan.) 1939.

101. Page, I. H.: Clinical Study of Malignant Hypertension, Ann. Int. Med. **12**:978 (Jan.) 1939.

course of the disease, while the vascular disturbances may be particularly outstanding, especially those in the vessels of the fundi. He noted that often the conduct and emotional stability of patients with malignant hypertension is quite in contrast to the emotional instability sometimes seen in patients with so-called benign essential hypertension.

PATHOGENESIS

Wiggers [102] in a discussion of the dynamics of hypertension was in essential agreement in regard to the similarity between experimental hypertension and essential hypertension in man. He stated that hypertension may be produced experimentally by intracisternal injection of kaolin, by section of the moderator nerves, by damage to the kidneys by ligation of the ureters and by permanent constriction of the renal arteries. It is only the last procedure which is entirely certain to result in increased systolic and diastolic pressures. He stated: "A candid evaluation of the reported evidence inclines one to the belief that essential and renal hypertension in man are likewise basically due to unknown humoral agents, but that, as in transient hypertension of normal individuals, vasoconstriction of nervous origin may be superimposed periodically or permanently." He expressed the belief that failure of the moderator nerves cannot be responsible for the nervous factor. The experimental hypertension produced by section of the moderator nerves does not resemble human hypertension, whereas that of renal ischemia essentially does. He discussed the nature of peripheral resistance according to the concepts of central collective and effective peripheral resistance. The latter is the net resistance offered by all the arterioles collectively. The capillary and the venous resistance are of little or no importance as factors affecting central resistance during hypertension. In order to produce peripheral resistance sufficient to cause elevation in blood pressure such as that found in essential hypertension, there must be intensive narrowing of the small vessels in the splanchnic area. Organic lesions of these vessels are not sufficiently widely distributed to be effective. Functional constriction of the arterioles and prearterioles seems to be the essential factor. Wiggers advanced the hypothesis that both in experimental and in human hypertension the functional constriction is not limited to the arterioles but pertains to the entire arterial tree, with constriction of all the muscular elements. This in the smaller arteries accounts for increased peripheral resistance, while in the larger vessels capacity and extensibility are reduced. This would account for the lengthening of pulse pressure which occurs in all cases of hypertension. Diminished elasticity of the aorta and its

102. Wiggers, C. J.: The Dynamics of Hypertension, Am. Heart J. **16**:515 (Nov.) 1938.

larger branches results in increased elevation of the systolic pressure and some lowering of the diastolic. It certainly occurs in atherosclerosis but probably occurs to some extent also when there is little or no sclerotic change in the vessels.

Pickering [103] in a theoretic discussion of high blood pressure in man agreed essentially as to the relationship between chemical and nervous factors and the cause of hypertension. He was inclined to believe that all areas are subject to arteriolar constriction and essentially to the same degree. He expressed the opinion that local arterial spasm such as has been thought to occur in hypertensive encephalopathy cannot occur. In his discussion he stated the belief that there is unanimity in regard to the presence of functional vasoconstriction as the essential cause of the disorder. That this is of humoral or chemical origin in its essential details seems to be supported by the weight of the evidence which Pickering advanced. The absence of a demonstrable pressor substance in hypertensive persons is a disturbing consideration. It can be explained only on the basis that the pressor substance is fixed immediately in the vessels or that it is present in very minute quantities.

Katz and Leiter [104] correlated the physiologic and clinical features of essential hypertension. They found most writers in agreement in regard to the relationship of increased peripheral resistance to increased arterial pressure and stated that they were essentially in accord with the advocates of this view except that they believed that the nervous control of the peripheral vessels is perhaps more important than the physical and chemical influences which control the peripheral arterioles. The peripheral resistance may be mediated locally in the arterioles by way of an axon reflex or through the peripheral autonomic ganglions, the dorsal root ganglions or the sympathetic and parasympathetic systems in general. Correlating such effective pathways are the vasomotor nerve centers of the spinal cord, medulla and higher centers of the brain. Both humoral and nervous impulses may be effective in initiating responses in these centers. Impulses arrive along the afferent nerves from the special sense organs, viscera and cardiovascular structures themselves. These may be mediated by any part of the cardiovascular system because, according to Katz and Leiter, the vascular end organs are not limited to the carotid arteries and the aorta but are found rather widely distributed in the large vessels. The most important end organs are those located in the carotid sinus. These and the associated nerve supply constitute the moderator mechanism and play a most important part in normal control of blood pressure. Hyper-

103. Pickering, G. W.: The Problem of High Blood Pressure in Man, Proc. Staff Meet., Mayo Clin. **14**:310 (May 17) 1939.

104. Katz, L. M., and Leiter, L.: Present Conception of Hypertension, Psychosom. Med. **1**:101 (Jan.) 1939.

tension may result from one of two types of causes, either an abnormal moderator mechanism, with loss of ability to control the effects of ordinary stimulation, or a normal moderator mechanism subjected to successive stresses exceeding the ability of this mechanism to cope with them. It is stated that an inherent weakness of this mechanism is its ineffectiveness in response to a chronic, persistent elevation of pressure. An abrupt transitory stimulus to the moderator end organs is much more effective. In the presence of arteriosclerosis and the diminution of distensibility of the vessel walls which results, the response may be much reduced. There is no evidence to indicate that the moderator mechanism is defective in hypertension, but it seems likely that in this disease it is exposed to excessive strain which is beyond its capacity to control. The authors agreed that all types of hypertension may be viewed as the result of a disproportion between strain on the moderator mechanism and its ability to cope with such stresses.

They likewise agreed that it does not seem probable that there are any changes in the fundamental hemodynamics of the circulation. All parts of the arterial system are involved more or less to the same degree.

Errors in classifying elevations of blood pressure are to be avoided, and those types of increased pressure secondary to arteriosclerosis, hyperthyroidism and other conditions with high systolic and low or normal diastolic pressures must be eliminated to justify the diagnosis of essential hypertension.

In discussing the mechanism of essential hypertension these writers pointed out that changes in diameter of the small peripheral vessels may easily be overlooked on microscopic examination and that very minute changes may have a profound influence on the blood pressure. Relatively small, superficially not apparent changes in tone of the smooth muscle of many peripheral vessels may result in a sufficient increase in peripheral resistance to produce and maintain an elevation of blood pressure. It is necessary that the peripheral vascular narrowing be universally distributed to maintain hypertension. Neurogenic strains on the moderator mechanism may be brought about by excessive stimulation of the vasomotor apparatus arriving from the sensorium and higher centers of the brain. Hyperactivity of the vasomotor centers brought about by disease or disturbances in the blood supply to the centers may result in increased stimulation of the moderator mechanism. Hyperactivity of the effective mechanism in the myoneural junctions of the smooth muscle of the peripheral blood vessels may exist, but there is no direct evidence to support the view that such increased neurogenic stimulation is constant or complete. Hypertension may be produced by a third method, namely, strains on the moderator mechanism of humoral origin, such as that observed in hyper-

plasia or tumor of the adrenal cortex. However, there is no evidence to prove that the substances arising from the hypophysis or from the adrenal cortex or from the kidney which produce sustained elevation of blood pressure are mediated by this mechanism. The authors stated that the assertion that there is a causal connection between impairment of renal blood supply and high blood pressure cannot be refuted. If this impairment is not primarily of an arteriosclerotic or other organic cause, it must be on the basis of functional renal vasoconstriction. How this vasoconstriction arises and how it mediates the development of hypertension are still unknown. There is at present no way of demonstrating the presence of renal vasconstriction early in hypertension.

Weiss [105] in his recent review quoted freely from the review of Sodeman, but he expressed the opinion that hypertension is a constitutional disorder in which both hereditary vasospastic and environmental factors are of considerable importance.

Alexander [106] stated that a definite correlation can be found between emotional tensions and fluctuations of blood pressure. In the observation of a patient suffering from chronic mental depression and essential hypertension it was found that when the patient was in an exceptionally calm mental state his blood pressure was somewhat lower and showed smaller fluctuations, with a downward tendency of the average level of blood pressure during the period of treatment. A psychologic reaction in patients with hypertension is generally admitted, and a general hypertensive type of personality has been suggested. Observations on psychic factors in hypertension have been recorded by several other writers (Miller;[107] Saul[108]). It seems reasonable to believe that such variations in blood pressure as these authors described are only those noted in normal persons and probably are not related to the genesis of hypertension.

In reporting observations on a group of patients with hypertension, Emerson and Irving [109] stated that "being above the ideal weight" was apparently associated with hypertension. They indicated that the by-products of the incomplete metabolism that accompanies habitual overeating were more likely to be factors in the elevation of blood

105. Weiss, E.: Recent Advances in Pathogenesis and Treatment of Hypertension: A Review, Psychosom. Med. **1**:180 (Jan.) 1939.

106. Alexander, F.: Psychoanalytic Study of a Case of Essential Hypertension, Psychosom. Med. **1**:173 (Jan.) 1939.

107. Miller, M. L.: Blood Pressure Findings in Relation to Inhibited Aggressions in Psychotics, Psychosom. Med. **1**:162 (Jan.) 1939.

108. Saul, L. J.: Hostility in Cases of Hypertension, Psychosom. Med. **1**: 153 (Jan.) 1939.

109. Emerson, W. R. P., and Irving, J. G.: Hypertension and Health Diagnosis: Study of One Hundred Cases, J. A. M. A. **111**:1174 (Sept. 24) 1938.

pressure than the increase in weight itself. They stated that the chief cause of hypertension in a group of patients who were not overweight was found in their faulty habits in regard to eating. Most of the patients discussed showed rather moderate increases in blood pressure and probably did not have true essential hypertension. Apparently systolic pressures only were considered, and while observations on systolic pressures may be of some importance in examinations with regard to health, there is apparently little reason to consider them from the point of view of hypertension. The increases in pressure observed were in many instances but little above the average normal for systolic pressure. By continued treatment with control of diet and correction of faulty habits the pressures of the patients under observation apparently fell to lower levels. The authors concluded that in their experience hypertension is a symptom which is frequently the result of faulty health habits rather than the result of physical defects. It is probable that patients with essential hypertension subjected to such measures would show variations in pressure, but it is very unlikely that the diastolic pressure could be reduced to normal or that it would remain normal.

It is interesting to note that Hines [110] has been able to observe blood pressure determinations on 1,185 persons from ten to twenty years after initial readings. In the great majority of those with elevation of blood pressure on the original readings hypertension had subsequently developed, whereas only a very small percentage of those who had relatively normal readings originally had acquired hypertension in the interval. He expressed the opinion that this is an indication that instability of blood pressure is a precursor of hypertension.

Engle and Binger [111] reported on the effect of acetylbetamethylcholine injected subcutaneously into normal and into hypertensive subjects. It was found that in the normal persons there was no significant fall in arterial pressure, while significant decreases occurred in almost every one of the hypertensive subjects. When this experiment was repeated on normal dogs and dogs with experimental renal hypertension, no differences were apparent. This seemed to indicate that the usual type of essential hypertension in man is of a different type from that of renal ischemia.

The writers suggested as a hypothesis that a deficient acetylcholine vasodilator mechanism may be a factor in the production of the arterial hypertension of man.

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110. Hines, E. A.: The Prognostic Significance of Hyperreactibility of the Blood Pressure in Normal Subjects, J. A. M. A. **112**:1016 (March 11) 1939.

111. Engle, D. E., and Binger, M. W.: The Blood Pressure Response of Hypertensive Patients to Acetyl-Beta-Methylcholine, Proc. Staff Meet., Mayo Clin. **14**:341 (May 31) 1939.

Keith, Wagener and Barker [112] in a study of a large group of cases of hypertension found that these cases could be placed in a definite classification according to the degree of severity of the disease and its clinical course. In the cases placed in group I the condition was symptomatic and without impairment of cardiac or renal functions. Age was not a factor, and biopsy of the pectoral muscle showed little alteration in the thickness of the walls. Group II consisted of cases in which the increase in pressure was more sustained. The retinal arterioles showed more changes than were observed in group I, but there was no retinitis. The cardiac and renal functions were likewise not impaired. More frequent arteriolar changes were noted in the muscles. In group III the disease was more severe. The pressure was high and sustained. The peripheral arteries were thick and easily palpable. The cardiac and renal functions were somewhat impaired. Cerebral symptoms were frequent. Angiospastic retinitis was more common, but edema of the disk was not present. Often marked changes were found on biopsy of the arterioles of the muscles. The prognosis was serious. In group IV the condition was grave. Cerebral, cardiac and renal symptoms were often marked. The fundi showed marked angiospastic retinitis. Severe headaches, pains in the muscles and gross hematuria were outstanding symptoms. Biopsy of the pectoral muscle showed variable degrees of change. A progressive angiospastic mechanism seemed to be the outstanding feature.

Heymans [113] reviewed the methods of production of experimental hypertension. In addition to section of the cardioaortic and carotid sinus moderator nerves, injection of kaolin into the cerebral ventricles and production of renal ischemia, another method is the administration of very large doses of vitamin D to dogs. This produces progressive increase in arterial blood pressure with development of arteriolar lesions characterized by necrosis of the endothelium, observed particularly in the kidney but present also elsewhere.

By producing constriction of the renal artery Wilson and Pickering [114] were able to produce acute arterial lesions in rabbits which in many were structurally identical with those of malignant hypertension. The degree of hypertension seemed to be the essential factor. The greatly raised intra-arterial pressure seemed to be the chief determinant

112. Keith, N. M.; Wagener, H. P., and Barker, N. W.: Some Different Types of Essential Hypertension: Their Course and Prognosis, Am. J. M. Sc. **19**:331, 1939.

113. Heymans, C.: Experimental Arterial Hypertension, New England J. Med. **219**:154 (Aug. 4) 1938.

114. Wilson, C., and Pickering, G. W.: Acute Arterial Lesions in Rabbits with Experimental Renal Hypertension, Clin. Sc. **3**:343, 1938.

of these lesions. The defects were particularly severe in the viscera except that there were no defects in the kidney the artery of which had been constricted.

In addition to other methods for the production of hypertension, Nowak and Walker [115] reported that ligation of the arteries to the brain producing cerebral ischemia led to hypertension. Such ligation must be carefully done.

Fatherree and Hines [116] observed the blood pressure response to epinephrine administered intravenously to patients with normal blood pressure and to others with hypertension. Their observations corroborated those of other workers. The effect of epinephrine on patients with hypertension is essentially no different from that on normal persons. Furthermore, relatively little change in diastolic pressure was noted.

Holman and Page [117] in studying the mechanism of experimental hypertension in dogs found the cardiac output to be unchanged both before and after the production of hypertension by constriction of the renal arteries.

Heumans' [118] studies on the hypertension produced in dogs by the induction of renal ischemia suggested that the humoral factor increases the excitability of the peripheral blood vessels to vasomotor constrictor stimuli. Peripheral vasconstriction occurs as well as a disturbance in the physiologic mechanism which normally regulates blood pressure.

Glenn, Child and Page [119] demonstrated that there is no definite relationship between the central nervous system and the maintenance of hypertension induced by renal ischemia. In a series of animals in which hypertension had been produced destruction of the spinal cord was followed by a sharp fall in blood pressure, which subsequently rose to a level above that of normal for the animal but not to the previous maximal levels.

Hessel [120] made some careful studies of the physical and chemical reactions of renin (a kidney extract). He found definite differences in action between this and other pressor substances as far as action

115. Nowak, S. J. G., and Walker, I. J.: Experimental Studies Concerning the Nature of Hypertension, New England J. Med. **220**:269 (Feb. 16) 1939.

116. Fatherree, T. J., and Hines, E. A., Jr.: The Blood Pressure Response to Epinephrine Administered Intravenously to Subjects with Normal Blood Pressure and to Patients with Essential Hypertension, Am. Heart J. **16**:66, 1938.

117. Holman, D. V., and Page, I. H.: The Cardiac Output in Arterial Hypertension, Am. Heart J. **16**:321 (Sept.) 1938.

118. Heumans, C.: Some Aspects of Blood Pressure Regulation and Experimental Arterial Hypertension, Surgery **4**:487, 1938.

119. Glenn, F.; Child, C. G., and Page, I.: Effect of Destruction of the Spinal Cord on Hypertension Artificially Produced in Dogs, Am. J. Physiol. **122**:506, 1938.

120. Hessel, G.: Concerning Renin, Klin. Wchnschr. **17**:843, 1938.

on smooth muscle is concerned. He observed continuous hypertension in rabbits as a result of daily injections of renin over a period of five weeks. This hypertension persisted for as long as seven months after the injections were discontinued. He was also able to demonstrate the presence of a pressor substance in blood obtained from a renal vein of a dog in which this vein previously had been clamped. These findings may have considerable significance.

The action of renin seems to be directly on the vascular tree. A rise in pressure was observed by Merrill, Williams and Harrison.[121a] The pressor response was not altered by removing the kidneys immediately before the injection, but a greater rise was obtained if nephrectomy was done two or three days prior to removal of these organs.

Tyramine, as well as renin,[121b] causes a rise in blood pressure in dogs and rats, with diminution of blood flow and shrinkage of the kidneys and little or no change in renal volume. Renin was found to cause a decrease in renal blood flow, swelling of the kidneys and an increase in the output of urine.

Grossman and Williams [121d] found that the kidneys of young rats had a higher content of renin than the kidneys of older ones, but the aged animals showed a more marked pressor response to renin.

Major [122] continued his observations on the presence of guanidine or a similar substance in the blood of persons with hypertension and again expressed the belief that there is present in their blood a greater amount of some such substance than is present in the blood of normal persons.

Katz and his associates [123] made long-continued observations on the hypertension produced by renal ischemia in dogs. They corroborated the observations of Goldblatt and others. There are several points of particular interest in their work. They found that variability in the duration of hypertension was not completely dependent on degree of occlusion alone but in part on functional integrity of the other kidney. The way in which this effect is brought about is uncertain. The hypertension is increased and prolonged if the second kidney is removed.

121. (*a*) Merrill, A.; Williams, J. R., Jr., and Harrison, T. R.: The Site of Action of the Renal Pressor Substance, Am. J. M. Sc. **196**:23 (July) 1938; (*b*) The Effects of a Pressor Substance Obtained from the Kidneys on the Renal Circulation of Dogs and Rats, ibid. **196**:240 (Aug.) 1938. (*c*) Williams, J. R., Jr.; Wegria, R., and Harrison, T. R.: Relation of Renal Pressor Substance to Hypertension of Hydronephrotic Rats, Arch. Int. Med. **62**:805 (Nov.) 1938. (*d*) Grossman, E. B., and Williams, J. R., Jr.: Relation of Age to Renal Pressor Substance, ibid. **62**:799 (Nov.) 1938.

122. Major, R. H.: Blood "Guanidine" in Arterial Hypertension: A Review of Eight Hundred Cases, Arch. Int. Med. **62**:946 (Dec.) 1938.

123. Katz, L. N.; Friedman, M.; Rodbard, S., and Weinstein, W.: Observations on the Genesis of Renal Hypertension, Am. Heart J. **17**:334 (March) 1939.

Under these conditions uremia may develop. They found that bilateral and sometimes unilateral nephrectomy was followed by transitory hypertension which they considered to be of neurogenic origin. Interesting cross transfusion experiments of eighteen hours or more were carried on between dogs having persistent renal hypertension and bilaterally nephrectomized animals. No rise in blood pressure occurred in any of the nephrectomized dogs, indicating the absence of a pressor substance in the blood or its presence in extremely small quantities or perhaps its marked lability. The perfusion of heparinized blood in large quantities from an anesthetized dog with renal hypertension into an isolated denervated hindlimb preparation failed to show the presence of any pressor substance.

Hoerner, Fontaine and Mandel [124] studied the effect of experimental hypertension of nonrenal origin on the kidneys of dogs. They induced hypertension by section of the moderator nerves of the carotid sinus and the aortic depressors according to the method of Heymans. They found that they could produce by this method a permanent form of hypertension. Eighteen to twenty-four months later they tested the renal function of these dogs and found no clinical evidence of impairment. They then performed unilateral nephrectomy, and histologic examination of these kidneys failed to show any lesion which could be attributed to hypertension.

Prinzmetal, Friedman and Abramson [125] obtained saline extracts of ischemic kidneys and found that greater pressor effects followed the use of these extracts than that of extracts of the contralateral control kidneys. Similar extracts of spleen and muscle exhibited no pressor qualities. Saline extracts of the kidneys of 21 patients with hypertension produced more definite pressor effects than extracts of the kidneys of persons who had normal blood pressures.

Cross transfusion experiments made by Friedman and Prinzmetal [126] on patients with malignant hypertension and normal persons failed to show any evidence of significant change in blood pressure. Blood plasma from a patient who had an adrenal pheochromocytoma had a marked effect when injected into the ear vein of a rabbit.

Rabbits' ears perfused with plasma from patients with hypertension revealed no pressor effect, nor did blood or plasma obtained from dogs with renal ischemia. In fact, a depressor effect was sometimes noted.

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124. Hoerner, G.; Fontaine, R., and Mandel, P.: Permanent Arterial Hypertension Obtained by Section of Regulators of Pressure and Its Action on Kidney, Arch. d. mal. du cœur **31**:1079 (Nov.) 1938.

125. Prinzmetal, M.; Friedman, B., and Abramson, D. I.: The Nature of Arterial Hypertension with Special Reference to the Role of the Kidney, Ann. Int. Med. **12**:1604, 1939.

126. Friedman, B., and Prinzmetal, M.: Vasomotor Effects of Blood in Patients with Hypertension and Animals with Experimental Hypertension, Ann. Int. Med. **12**:1617, 1939.

ENDOCRINE TYPES OF HYPERTENSION

Hypertension, both of the paroxysmal and of the persistent type, in association with disease of the adrenal glands had been reported previously by Nuzum and Dalton. They have now reported 2 additional cases.[127] One of the patients, 62 years of age, became decompensated, with low blood pressure. Subsequently hypertension gradually developed over a period of a month. The increased pressure was maintained for several months, until death. At autopsy there was marked hyperplasia of the adrenal cortex as well as cortical adenoma. The second patient presented a picture fairly typical of chronic pheochromocytoma. The authors discussed and reviewed the previously reported cases of hypertension associated with adrenal tumor or disease.

Similar cases are being reported with increasing frequency as the clinical syndrome becomes better known and the condition is considered by clinicians (Brunschwig, Humphreys and Roome;[128] Palmer and Castlemen).[129]

Bisgard,[130] studying a group of patients with hyperthyroidism, found two types of associated hypertension. In these patients the blood pressure was usually significantly elevated above that which might be expected on the basis of hyperthyroidism alone. In some of the patients the elevation in blood pressure was not influenced by thyroidectomy, although symptomatic relief occurred. The blood pressure, both systolic and diastolic, remained high. In a second group, after thyroidectomy both systolic and diastolic pressures receded to a lower level, either normal or nearly normal, where it usually remained; in some of the patients there was a subsequent rise. There was an abnormal response to the cold pressor test in these patients, as well. Bisgard expressed the belief that the relationship of hyperthyroidism to hypertension in such patients is merely provocative, that hyperthyroidism merely exaggerates or precipitates latent hypertension. No relationship was found between the height of the maximal arterial blood pressure and basal metabolism.[131]

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127. Nuzum, F. R., and Dalton, J. W.: Paroxysmal and Persistent Hypertension in Association with Lesions of the Adrenal Glands, Am. Heart J. **16:** 643 (Dec.) 1938.

128. Brunschwig, A.; Humphreys, E., and Roome, N.: Relief of Paroxysmal Hypertension by Excision of Pheochromocytoma, Surgery **4**:361, 1938.

129. Palmer, R. S., and Castlemen, B.: Paraganglioma (Chromaffinoma, Pheochromocytoma) of Adrenal Gland Simulating Malignant Hypertension: Report of Case, New England J. Med. **219**:793, 1938.

130. Bisgard, J. D.: Relation of Hyperthyroidism to Hypertension, Arch. Int. Med. **63**:497 (March) 1939.

131. Reznitskaya, E. Y., and Spivak, P. Y.: Basal Metabolism in Hypertension, Klin. med. **16**:1410, 1938.

Van Bogaert and van Baarle [132] studied the relationship of hypertension to the hypophysis. They examined the spinal fluid of 19 patients and found no evidence of the presence of estrogenic substances except in the fluid from a patient with eclampsia who presented obesity and hypertrichosis. They concluded that there was no direct cause and effect relationship between hypertension and hypophysial disease.

Kylin and von Koranyi [133] expressed the belief that the theory of the pituitary origin of hypertension and diabetes has been strengthened as a result of their observations on rabbits into which pituitary glands were transplanted. They found a rise in blood pressure in such animals. The blood pressure fell after a period of several months only to rise again to rather high levels after an interval of six months.

Blood Pressure–Raising Reflexes.—Of the blood pressure–raising reflexes, the one most frequently studied and best known is the cold pressor test of Hines and Brown. Recently Hines [134] called attention to the fact that various investigators using this test have varied the technic and have yet used the criteria of Hines and Brown for interpreting the results. Hines expressed the opinion that any significant change in technic should be attended by the establishment of a new set of standards. He held that the technic is being incorrectly applied, and as a consequence variations in results are being reported. Hines listed certain precautions to be observed in carrying out the test. The subject should be lying down. If other positions are used, the effect of posture should be considered. Apprehension on the part of the subject should be prevented by a careful explanation of what is to be done. The subject should not have taken sedatives or vasodilator drugs within a period of twenty-four hours. The subject is allowed to rest in a quiet room for twenty to sixty minutes. Several readings of blood pressure are taken until a basal level has been approximated. In the presence of hypertension a longer period of rest may be necessary. The cuff of the sphygmomanometer is applied to one arm, and the opposite hand is immersed to just above the wrist in ice water. The temperature of the bath should be 4 C. With the hand still in the water, readings of blood pressure are taken at the end of thirty and sixty seconds. The higher of the two readings obtained while the hand is in the water is taken as an index of the response. As soon as the sixty second reading has been made, the hand is removed from the ice water. Readings are

132. Van Bogaert, A., and van Baarle, F.: Hypertension artérielle et hormones hypophysaires vasopressives et gonadotropes, Acta med. Scandinav. **96**:56, 1938.

133. Kylin, E., and von Koranyi, A.: Studies on Blood Pressure and Blood Sugar in Rabbits into Which Pituitary Glands Were Transplanted, Klin. Wchnschr. **17**: 668, 1938.

134. Hines, E. A., Jr.: Technic of the Cold Pressor Test, Proc. Staff Meet., Mayo Clin. **14**:185, 1939.

taken every two minutes until the blood pressure returns to its previous level. The maximal response usually occurs within thirty seconds, and in a normal subject the pressure usually returns to a basal level within two minutes after the hand has been removed from the cold water. The return is often delayed in the presence of established hypertension. The diastolic response is more reliable than the systolic. Both systolic and diastolic readings should be considered. Inasmuch as the test is a measure of vasoconstrictor tone, the diastolic reading alone is not an adequate criterion. According to Hines's observations, a systolic rise of 20 mm. of mercury with a diastolic rise of 15 mm. or more indicates hyperreactivity. A maximal rise of above 140 mm. of mercury systolic and 90 mm. diastolic is definite evidence of hyperreactivity of the vasoconstrictor mechanism.

Hines and Roth [135] observed the effect of tobacco on the blood pressure as measured by a standard smoking test. A rise in blood pressure was noted in the majority of persons tested. Successive rises resulted after smoking only in subjects who had evidence of inherent hyperreactivity of the vascular system as measured by the cold pressor test. They expressed the opinion that these observations should be interpreted as indicating that this is not the result of a known specific stimulus acting on a hyperreactive vascular system but is the result of the presence of some substance in tobacco smoke which directly causes vasoconstriction.

Hammer and Schulte [136] have made observations of the effect on blood pressure of prostatic massage. Among 378 patients, there was an increase in systolic and diastolic pressure in 75 per cent, while in 23 per cent there was a decrease. There was an increase in pulse rate in all. With 50 subjects in whom these results were observed the cold pressor test was also done. The rise in blood pressure observed was greater, as was the increase in pulse rate, following prostatic massage than in the cold pressor test. In a fair proportion of the subjects a hyperresponse occurred following each procedure. This result is similar to that observed following cold and tobacco smoking.

As another type of reflex, Moore and Allen [137] made some observations on the carotid sinus reflex in hypertension. They found some variation in different groups of hypertensive persons and expressed the belief that elevation of blood pressure may have different mechan-

135. Hines, E. A., Jr., and Roth, G. M.: The Effect of Tobacco on the Blood Pressure as Measured by a Standard Smoking Test, Proc. Staff Meet., Mayo Clin. **13**:524 (Aug. 17) 1938.

136. Hammer, H. J., and Schulte, T. L.: Changes in Blood Pressure Produced by Prostatic Massage, J. A. M. A. **111**:308 (July 23) 1938.

137. Moore, F. H., and Allen, E. V.: Vascular Clinics: Carotid Sinus in Hypertension, Proc. Staff Meet., Mayo Clin. **13**:747, 1938.

isms. In these groups they found in the presence of hypertension a rough parallelism between the effect of carotid sinus pressure and the effect of the administration of vasodilator and sedative drugs. Carotid sinus pressure, therefore, may be used as an additional method for the determination of the liability of blood pressure.

The work of Alam and Smirk [138] concerning the blood pressure–raising reflexes in health and in hypertension is of considerable interest and importance. In the past year they continued observations similar to those previously reported. An important blood pressure reflex was demonstrated in their work. This consists of exercise of the muscles of an extremity performed during arrest of circulation. Such a procedure results in a general systemic rise of blood pressure as well as in the production of pain in the exercised muscles. The elevation in blood pressure and the pain in the muscles both persist after cessation of the exercise if the circulation to the extremity remains arrested. Both results are proportional to the amount of exercise during the ischemia. The rise in blood pressure is of reflex origin and occurs before the appearance of pain in the exercised muscles.

Various other sensory stimuli for the production of pain were employed. Some of these cause much pain but little rise in blood pressure; others cause less pain but produce some increases in systemic pressure. Reflex increases of blood pressure were found to be set up by impulses arising from voluntary muscle which failed to cause pain or discomfort. Rises in blood pressure in the same person under similar conditions showed no correlation with the amount of pain. They concluded that the reflex rise in blood pressure resulting from this procedure is not dependent on the pain produced. The effect of these procedures was observed in a patient having a lesion of the spinal cord in whom there was an interruption of the sensory pathway in the affected extremity. Exercise of this extremity during the circulatory arrest resulted in no elevation in blood pressure, while in the normal extremity the usual rise occurred. It would seem that the authors are correct in concluding that their observations in this case confirm the belief that such increase in blood pressure is the result of a reflex which results from the accumulation of metabolites in the muscles of a normally innervated leg.

These investigators studied this reflex in persons with hypertension of the essential type as well as in those having definite renal disease. They employed, in addition, the cold pressor test with immersion of

138. Alam, M., and Smirk, F. H.: (*a*) Blood Pressure Raising Reflexes in Health; Essential Hypertension, and Renal Hypertension, Clin. Sc. **3**:259 (Aug.) 1938; (*b*) Unilateral Loss of a Blood Pressure Raising, Pulse Accelerating Reflex from Voluntary Muscle Due to a Lesion of the Spinal Cord, ibid. **3**: 247 (Aug.) 1938; (*c*) Observations in Man Concerning the Effects of Different Types of Sensory Stimulation upon the Blood Pressure, ibid. **3**:253 (Aug.) 1938.

two thirds of the forearm and the arrest of circulation. Circulatory arrest during immersion caused the temperature of the arm to fall more rapidly than when the circulation was free, because the degree of cold attained was dependent on the rate of flow of blood through the arm. They pointed out that under the conditions of circulatory arrest the actual stimulus is of constant intensity, and its effectiveness varies according to the sensitivity of the subject to cold. This method was compared with exercise of an ischemic limb. With normal persons both blood pressure–raising reflexes were found to be greater in their effect in old than in young subjects when the systolic blood pressure alone was observed. The rise in diastolic pressure was approximately the same for both age groups. In persons who had chronic nephritis with hypertension the effects on both systolic and diastolic pressures were found to be less than those observed in normal subjects of the same age group. Large rises in pressure were more frequent in the patients with essential hypertension than in normal controls of the same age group. However, large rises were found in a few normal subjects, and only small rises occurred in some persons with hypertension. This would indicate that high reactivity to such a blood pressure–raising reflex cannot by itself explain a high level of resting blood pressure. Such a high degree of reactivity may express itself, therefore, in daily life by remarkable variations in blood pressure. This may, perhaps, sometimes lead to permanent hypertension. The writers stressed the fact that the average blood pressure of subjects showing a high degree of reactivity is no greater than the average blood pressure of subjects with a low degree of reactivity. They found the incidence of high reactivity among their patients in an Egyptian hospital practice much greater than the incidence of hypertension.

In normal subjects exercise of an ischemic arm resulted in either no change or slight slowing of the pulse rate. In patients with hypertension the pulse rate usually increased. This is in contrast to what is usually observed. This reversal of the blood pressure–pulse rate relationship in hypertension might be of considerable importance if it could be shown to be due to a change in the reactions of a depressor mechanism.

Thus it would seem that such blood pressure–raising reflexes are to be regarded as indicators of a hyperreactive state of the vasomotor mechanism rather than as an essential part of the mechanism of the production of essential hypertension, unless it may be considered that such a tendency toward vasoconstriction is the precursor of the actual change which results in hypertension. The blood pressure–raising reflex of Alam and Smirk is interpreted by them as being one of the natural defensive mechanisms of the body, designed to increase the rate of blood flow through fatigued muscles by raising the general blood pressure.

Normal persons and persons with hypertension were subjected to inhalation of carbon dioxide by Hardgrove, Roth and Brown.[139] The pressor reaction from this procedure was determined in both groups. A definite rise in blood pressure was found. There were no significant differences in the two classes of persons except that with the application of cold there was a greater rise in pressure in those with hypertension, particularly if the condition was in the early stages. In the more advanced stages this rise was less marked. Such an observation might be the result of reflex transmission of a peripheral stimulus to a more highly reactive vasomotor center in the hypertensive person. Why this should occur is still obscure.

Leiter[140] reported 2 unusual cases of renal hypertension. One of the patients was a man of 40 who showed a rise of systolic and diastolic pressure. Only four months elapsed between the first rise in blood pressure and the patient's death. At autopsy extensive atrophy was noted in the kidneys, which apparently was dependent on occlusion of the corresponding arcuate and interlobar arteries. The occlusion of these vessels was apparently sufficient to result in ischemia of at least portions of the kidney, and thus the condition appeared to be similar to the Goldblatt type of experimental hypertension. The cause of the arterial disease is not clear, although the patient had syphilis. In the other patient the analogy to experimental hypertension was still more striking in that the left renal artery was completely occluded by an arteriosclerotic plaque and the right renal artery was markedly narrowed. Apparently hypertension in this case had persisted over a long period.

Similar cases are being reported with increasing frequency, such as the one described by Blatt and Page,[141] in which the renal arteries were constricted by a lymphosarcoma. Freeman and Hartley[142] observed a patient with hypertension who had a solitary, ischemic kidney.

Schroeder and Steele[143] found some abnormality of the urinary tract in 50 of 79 patients with hypertension. They were able to demonstrate these defects by means of intravenous pyelograms. This seems to be an astonishingly high proportion showing renal involvement with

139. Hardgrove, M.; Roth, G. M., and Brown, G. E.: The Pressor Reaction Produced by Inhalation of Carbon Dioxide: Studies of Patients with Normal Blood Pressure and with Hypertension, Ann. Int. Med. **12**:483, 1938.

140. Leiter, L.: Unusual Hypertensive Renal Disease: Occlusion of Renal Arteries (Goldblatt Hypertension); Anomalies of Urinary Tract, J. A. M. A. **111**:407 (Aug. 6) 1938.

141. Blatt, E., and Page, I. H.: Hypertension and Constriction of the Renal Arteries in Man: Report of a Case, Ann. Int. Med. **12**:1690, 1939.

142. Freeman, G., and Hartley, G., Jr.: Hypertension in Patient with Solitary Ischemic Kidney, J. A. M. A. **111**:1159 (Sept. 24) 1938.

143. Schroeder, H. A., and Steele, J. M.: Abnormalities of Urinary Tract in Essential Hypertension, Proc. Soc. Exper. Biol. & Med. **39**:107, 1938.

hypertension. No doubt such abnormalities occur with sufficient frequency in association with hypertension to make it necessary that they be considered in every case of this disease.

PATHOLOGY OF HYPERTENSION

Many writers have during the past hundred years considered the cause and effect relationship of the arteriolar changes found not only in the renal structures but in the general and systemic arterioles. Keith and his co-workers at the Mayo Clinic have been impressed with the relationship of alterations in the structure of the arterioles to hypertension. In the past year they continued their pathologic studies of the arterial system in severe hypertension and became convinced that, regardless what the cause of hypertension may be, in the later stages of the disease there are widespread arterial and particularly arteriolar lesions.

Odel [144] studied the structural changes in the arterioles of the myocardium in patients with hypertension in the malignant phase. These alterations they found to be similar to those described as occurring in the arterioles of the pectoral muscle. These changes do not occur with any degree of consistency and are not present in every such patient, and when they are found they are less marked in the myocardium than in other organs of the same person. There are also marked variations in the degree of change in different persons, as well as in various vessels of the myocardium of the same person. Chronic diffuse fibrosis was found to involve the myocardium of patients with malignant hypertension more commonly than that of patients having less severe types of arterial hypertension.

Morlock [145] studied the arterioles of the viscera in similar groups and found a definite increase in thickness of wall and reduction of the ratio of wall to lumen in the arterioles of hypertensive subjects. This was severe proportionally to the severity of the hypertension. Hyperplasia of the nuclear elements of the media appeared to be an earlier change, while degeneration and fibrosis occurred later. The arterioles of the pancreas, liver, gastrointestinal tract and spleen were observed. The contrast between these vessels in normal persons from youth to old age and those in hypertensive subjects was definite.

Rosenberg [146] reported on the cerebral vessels in patients with malignant hypertension and pointed out that in the brain as elsewhere

144. Odel, H. M.: Arteriolar Changes in the Myocardium in Diffuse Arteriolar Disease with Hypertension, Group IV, Proc. Staff Meet., Mayo Clin. **14**:210, 1939.

145. Morlock, C. G.: Arterioles of the Pancreas, Liver, Gastro-Intestinal Tract and Spleen in Hypertension, Proc. Staff Meet., Mayo Clin. **14**:214, 1939.

146. Rosenberg, E. F.: The Brain in Malignant Hypertension, Proc. Staff Meet., Mayo Clin. **14**:217, 1939.

in the body there is a definite separation of the findings in arteriosclerosis of the larger vessels and the vascular effects of hypertension. Two major pathologic processes which affect the brain of a patient with malignant hypertension are hemorrhage and thrombosis. In some cases small spotty hemorrhagic areas are distributed throughout the brain structure. These are usually associated with small infarctions. In other cases numerous minute capillary hemorrhages occur, often so small as to be seen only on microscopic examination. Such capillary hemorrhages are probably responsible for considerable irritation of the brain. Both large infarctions and multiple miliary infarctions were noted. Edema of the brain and increase in the quantity of intracranial fluid seemed to occur rather frequently. The finding of many small cortical lesions may furnish an explanation of the convulsions noted in many of these cases. Cerebral arterioles were found to be altered markedly in such cases of malignant hypertension. These changes resembled those found in the arterioles of other viscera and consisted of an increase in thickness of wall and a reduction of the ratio of wall to lumen. Cerebral phenomena of malignant hypertension, often designated as the cerebral crises of hypertensive encephalopathy and often ascribed to vasospasm, seem much more likely to be on the basis of such widespread destructive arteriolar or capillary lesions, either infarction or hemorrhage, or both. There is no anatomic evidence that vasospasm occurs. Vasospasm has been observed in the retinal arteries by ophthalmic examination, but in the opinion of Kernohan it does not persist sufficiently long to destroy nerve cells of the retina and impair vision. He likewise thinks that the thickening of the walls of the arterioles cannot be the cause of hypertension. This thickening is to be considered compensatory hypertrophy of the musculature of the media. When the walls have become sufficiently thick that nourishment is diminished, degeneration follows. Necrosis and liquefaction of the media may occur with lesser degrees of impairment of nutrition. Fatty degeneration may occur and minimal amounts of fibrosis develop. Endothelial proliferation is a late occurrence.

Rosenberg, Keith and Wagener[147] reported 2 interesting cases of widespread arterial disease. Both patients showed elevation of blood pressure. Diffuse arterial disease was the cause of death in both. In one the course was rapid and hypertension was sustained. The clinical manifestations were those referable particularly to the central nervous system, retina, heart and kidneys. The phenomena exhibited were on the basis of simultaneous involvement of the arterioles in all these

147. Rosenberg, E. F.; Keith, N. M., and Wagener, H. P.: Diffuse Arterial Disease with Hypertension: Two Unusual Cases of Contrasting Types, Arch. Int. Med. **62**:461 (Sept.) 1938.

structures—on the basis of spasm or of acute or chronic pathologic reactions in the majority of the arterioles. Fever and leukocytosis with marked toxemia and inflammatory-like lesions in the small arteries suggested that the disease was one of an infectious or toxic origin involving the arterioles and resulting in severe hypertension. In the second patient the clinical course was very much slower. The hypertension was rather mild, with the development of atherosclerotic lesions in the arteries. The disease picture terminated with the development of thromboses in the vicinity of the atheromatous lesions. The fundamental change in the second patient was that of arteriosclerosis. Hypertension in this patient was relatively mild, without marked increase in diastolic pressure, while in the first patient hypertension was severe and diffuse involvement of the arterioles was the outstanding defect. This is in contrast to Shapiro's case,[148] in which hypertension had been present for more than twenty-five years. At autopsy there were no alterations in the structure of the arterioles of the kidneys.

A CRITICAL REVIEW OF THE SURGICAL TREATMENT OF VASCULAR DISEASES

By Dr. de Takáts and Dr. Beck

The literature contains no report of drastic departures from accepted methods of treatment; some of the enthusiasm shown in the reports of previous years is giving way to sober evaluation of the results obtained. The importance of close cooperation between surgical and medical groups and the value of combining physical therapy, drug therapy and operative procedures are becoming more and more obvious.

PARAVERTEBRAL BLOCK

The treatment of patients with apoplexy by infiltration of the stellate ganglion with procaine hydrochloride, as originally conceived by Leriche, was evaluated by Mackey and Scott.[149] In 19 patients stellate infiltration was carried out by the posterior route, and 9 of them showed definite improvement. In 1 patient an inadvertent intravenous injection almost caused death from respiratory failure. In older patients with severe cerebral hemorrhages the method has failed. Patients with cerebral thrombosis may show some improvement. The ideal patient for this type of treatment is a young person with cerebral embolism. The injection should be given as soon as possible after the

148. Shapiro, S.: Report of Case of Essential Hypertension of More Than Twenty-Five Years' Duration Showing No Renal Arteriolar Changes at Autopsy, J. Lab. & Clin. Med. **24**:60, 1938.

149. Mackey, W. A., and Scott, L. D. W.: Treatment of Apoplexy by Infiltration of the Stellate Ganglion with Novocain, Brit. M. J. **2**:1 (July 2) 1938.

onset of apoplexy, as its purpose is to relieve the collateral edema around the vascular occlusion and thereby diminish the extent of residual damage. Only negligible improvement can be expected from treatment begun as late as twenty-four hours after the onset.

In our experience, the anterior approach for injecting the stellate ganglion is simpler. If the method is to become useful, it must be taught to the medical residents in hospitals, who can be ready to inject the ganglion on the side of the accident within a short time. Huge intraventricular hemorrhage, with increasing coma and Cheyne-Stokes respiration, will obviously be unaffected, as in 1 patient under our observation, but if intravascular or intraspinal injection is avoided the treatment should do no harm. The dramatic recoveries of some of the patients described by Mackey and Scott stimulate more extensive trial of the method.

In strict analogy with the idea of releasing collateral vasospasm and edema of the brain in cerebral thrombosis is the suggestion of Ochsner and DeBakey,[150] again based on the idea of Leriche, that thrombophlebitis causes edema not only because of venous and lymphatic block but because of a reflex spasm of veins, arterioles and arteries. This vasospasm manifests itself by a decrease in arterial pulsations, cooling of the digits and increased permeability of the vascular endothelium, which in turn leads to an outpouring of fluid high in protein. The authors reported 17 cases in which following one or several injections of procaine hydrochloride to the sympathetic chain a rapid disappearance of pain, fever and edema were observed. The patients got out of bed in a few days, and evidence was presented that no residual edema developed, in spite of the fact that no elastic support was prescribed. If this procedure can really prevent the cumbersome and painful thrombophlebitic indurations and ulcerations, it will mean a marked advance in the treatment of thrombophlebitic edema.

It should be pointed out, however, that not all patients show clinical evidence of such reflex spasm of vessels. In fact, some of them exhibit signs of vasodilation. To make paravertebral injections requires a certain amount of study and practice. A successful block of the sympathetic chain should be followed by a rise in the temperature of the skin and a cessation of sweating in the limbs whose sympathetic nerve supply is blocked.

In previous reviews we emphasized the importance of the spasm of collateral vessels when arterial pathways become suddenly obstructed; heat, suction and pressure as well as injections of papaverine hydrochloride have been recommended to overcome this reflex effect. When

150. Ochsner, E. W. A., and DeBakey, M.: Treatment of Thrombophlebitis by Novocain Block of Sympathetics, Surgery **5**:491 (April) 1939.

the interval of time for embolectomy has passed, arteriectomy may be proposed.[151] It might be worth while to add block of the sympathetic pathways to these methods as clearcut experiments have shown the protective effect of sympathectomy following arterial ligations.[152]

But the interruption of these vascular reflexes may have more than a temporary effect. Elsewhere one of us (G. de T.) drew attention to a group of reflex dystrophies[153] in which a reflex is activated by some focus of irritation, such as a thrombus; this reflex does not subside when the original exciting cause disappears but becomes a fixed, self-perpetuating mechanism leading to so-called traumatic edema, painful osteoporosis or Sudĕck's atrophy. It remains to be seen whether early interruption of these reflexes may not prevent the circulatory disturbances which are encountered following vascular accidents. Only recently Villaret and Cachera[154] studied the vasomotor phenomena of the brain consecutive to embolism and found that the vasomotor system was greatly disturbed, thus possibly contributing to the late sequelae of cerebral accidents.

Severe paroxysmal tachycardia, following appendectomy and leading within a few hours to cardiac failure, was sucessfully aborted by Leibovici, Dinkin and Wester[155] with an injection of procaine hydrochloride into the left stellate ganglion. The pulse promptly fell from 180 to 72, and the blood pressure, which had been gradually falling from 130 mm. systolic and 80 mm. diastolic to 80 mm. systolic and 50 mm. diastolic, also returned to normal. The 29 year old patient never had another attack, and an electrocardiogram taken a few weeks later showed no aberration from the normal. The authors collected 8 cases of sinus tachycardia and 5 cases of paroxysmal tachycardia in which ganglionectomy or injection of procaine hydrochloride was done. With the paroxysmal type the block of the sympathetic nerves was less successful than with the former. In this particular case, morphine, camphor, ouabain and quinidine were all tried, as well as ocular and carotid sinus compression, without avail, before block of the stellate ganglion was undertaken.

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151. Griffiths, D. L. E.: Arterial Embolism, Lancet **2**:1339 (Dec. 10) 1938.

152. Mulvihill, D. A., and Harvey, S. C.: Studies on Collateral Circulation: I. Thermal Changes After Arterial Ligation and Ganglionectomy, J. Clin. Investigation **10**:423 (Aug.) 1931.

153. de Takáts, G.: Reflex Dystrophy of the Extremities, Arch. Surg. **34**:939 (May) 1937.

154. Villaret, M., and Cachera, R.: Les répercussions vasculaires tardives de l'embolie cérébrale en pathologie expérimentale, Presse méd. **47**:267 (Feb. 18) 1939.

155. Leibovici, R.; Dinkin, L., and Wester: Accès post-opératoire grave de tachycardie paroxystique traité avec succès par la novocaïnisation du ganglion stellaire gauche, Presse méd. **47**:83 (Jan. 18) 1939.

PHLEBOTOMY FOR ILIOFEMORAL THROMBOSIS

Kulenkampff [156] reported 61 cases in which he probed and extracted a thrombus from the femoral vein through an opening in the saphenous. An analysis of his cases shows that in many the operation was premature or unnecessary, as little was found outside of thickened adventitia or periphlebitic exudate. Nevertheless in a well selected case, especially if a pulmonary shower has already occurred, the operation should be seriously considered, as sometimes the second or third embolus proves to be fatal. Our own experience with this method is limited, and more exact indications will have to be worked out in the future. The operation is easily performed, does not necessitate a venous suture and does not result in obstruction of the deep veins. Läwen [157] approached such a thrombus through an incision of the femoral or iliac vein with temporary proximal occlusion of the vein. This procedure requires a venous suture, and it seems to us that the chances of renewed thrombus formation are thereby greatly increased.

These two procedures undertaken for bland, static thrombi are not comparable to those reported in last year's review [158] for ligating veins proximal to septic thrombi. These were undertaken to prevent feeding of septic material into the blood stream.

USE OF HEPARIN IN SURGICAL OPERATIONS ON BLOOD VESSELS

Murray and Best [159] published the far reaching results of their animal experiments, which show that arterial anastomosis, venous graft into an arterial segment and arterial embolectomy can be readily performed without the formation of a thrombus, provided the animal has received sufficient amounts of heparin either in the local vascular segment or in the systemic circulation. According to Murray, embolectomy in man can now be performed even after the lapse of a day, since the reformation of the clot can be prevented by heparin.

Since the advent of the purified product, heparin can be safely administered to the patient intravenously. The ordinary intravenous drip is used, and to the salt solution sufficient heparin is added to increase the clotting time of the blood of the patient to about fifteen minutes. Usually heparin is added in the proportion of 10 units of

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156. Kulenkampff, D.: Die Verhütung schwerer und tödlicher Embolien durch Ausräumung der Vena iliaca, Arch. f. klin. Chir. **193**:727, 1938.

157. Läwen, A.: Weitere Erfahrungen über operative Thrombenentfernung bei Venenthrombose, Arch. f. klin. Chir. **193**:723, 1938.

158. Scupham, G. W.; de Takáts, G.; Van Dellen, T. R., and Beck, W. C.: Vascular Diseases: A Review of Some of the Recent Literature, with a Critical Review of the Surgical Treatment, Arch. Int. Med. **62**:482 (Sept.) 1938.

159. Murray, G. D. W., and Best, C. H.: The Use of Heparin in Thrombosis, Ann. Surg. **108**:163 (Aug.) 1938.

heparin to 1 cc. of salt solution; in the average patient this solution should run at about 25 to 30 drops a minute.

At present the expense of the material and the difficulties encountered in its shipment from Canada restrict the use of this highly significant product. Whether it will have wide application in the prevention and treatment of postoperative thrombosis, pulmonary embolism, coronary thrombosis and cerebral thrombosis is yet to be seen; in suturing of blood vessels, however, the indications for it are so clearcut and striking that its routine use will bring about marked improvement in results. The suturing of aneurysms and the closing of arteries from which emboli have been extracted are greatly facilitated by the use of heparin. This is a most important contribution to vascular surgery.

PROCEDURES FOR THE TREATMENT OF ANEURYSMS

Arteriovenous Aneurysms.—Reid and McGuire[69] analyzed 21 cases of arteriovenous and 9 cases of cirsoid aneurysm, and supplemented their analysis by experimental observations in dogs. In 16 of the cases of arteriovenous aneurysm operation was done, and in all except a case of pulsating exophthalmos the condition was cured. In 2 instances the aneurysm healed spontaneously. In all of the 9 cases of cirsoid aneurysm operation was done, and in 3 the condition was cured and in the other 6 it was more or less improved. There were no deaths in the entire series of 30 cases.

Their physiologic observations have been discussed in a previous part of this review. Extensive clinical observations were presented on cardiac damage, thinning and dilatation of the proximal artery, circulation time, blood volume, the bradycardic phenomenon on closure of the fistula, alterations in blood pressure, venous pressures and the extent of collateral circulation. In addition, there is a wealth of important technical suggestions. Two new methods of dealing with these exceedingly complicated arteriovenous fistulas are presented. In addition, the proper time to operate and the standard curative procedures are discussed.

Not only is this contribution a great source of information to the surgeon, but it emphasizes the extent to which the cardiac damage can be reversed by permanent closure of the fistula. It must be regarded, together with the previous articles of the senior author and those of Halsted, Matas and Holman, as the foundation of all present knowledge on the subject. It also contains a number of interesting data on the physiology of circulation.

Arterial Aneurysms.—A subclavian aneurysm producing gangrene of two fingers and caused by a cervical rib was reported in a young

woman in her early twenties.[160] Resection of the sac and removal of the supernumerary rib effected a cure. In a patient with a similar lesion, but who was much older, one of us (G. de T.) performed proximal and distal ligation of the artery with scalenotomy. We have come to regard a roentgenogram of the cervical spine as an almost routine procedure in any case of arterial obstruction of an upper extremity. Oblique views directed upward and medially will show such a rib most clearly. The study of 1,000 thoracic roentgenograms of children revealed an incidence of cervical rib in 1.2 per cent.[161] A cartilaginous connection between the seventh tranverse process and the first rib, however, will not be represented in roentgenograms.

Popliteal aneurysms are again receiving attention. While Kimpton and Sanderson[162] reported successful suture of such an aneurysm with imbrication in 2 cases, Yater[163] reported that in his cases the aneurysm ruptured and amputation became necessary.

Dandy[164] contributed another important article on the treatment of intracranial aneurysms. He presented 3 cases of aneurysm of the intracranial portion of the internal carotid artery. In each case the aneurysm was alongside the carotid artery as it came through the cavernous sinus. In each instance it was treated by trapping it between a proximal ligature—that of the internal carotid artery in the neck—and a distal ligature, placed intracranially, with the help of a silver clip. All the patients were symptomatically cured. He discusses the importance of arteriography for the localization of these lesions.

In studying this article one cannot escape the feeling that the rational treatment of intracranial aneurysms has just begun and great advances are to be expected in the future.

SYMPATHETIC GANGLIONECTOMY FOR PERIPHERAL VASCULAR DISEASE

Sunder-Plassmann,[165] well known for his extensive neurohistologic studies on the vegetative nervous system, stained the sympathetic ganglions removed at operations for Raynaud's disease with

160. Baumgartner, A.; Clerc, A., and Macrez, C.: Sur l'anévrysme artériel de voisinage et la gangrène ischémique des doigts en rapport avec les côtes cervicales: Leur traitement chirurgical, Presse méd. **46**:1665, 1938.

161. Davis, D. B., and King, J. C.: Cervical Rib in Early Life, Am. J. Dis. Child. **56**:744 (Oct.) 1938.

162. Kimpton, A. R., and Sanderson, E. R.: Popliteal Aneurysm: Report of Two Cases, New England J. Med. **220**:146, 1939.

163. Yater, W. M.: Rupture of Popliteal Aneurysm, read before the American Heart Association, St. Louis, May 13, 1939.

164. Dandy, W. E.: The Treatment of Internal Carotid Aneurysms Within the Cavernous Sinus and the Cranial Chamber, Ann. Surg. **109**:689 (May) 1939.

165. Sunder-Plassmann, P.: Die Raynaudsche Erkrankung und ihr Formenkreis, Deutsche Ztschr. f. Chir. **251**:125, 1938.

Bielschowsky's stain and found definite pathologic changes pointing to toxic damage of the ganglions, fibrils and terminal reticulum. Allergic phenomena may also be at play. He expressed the belief that sympathectomy is not real denervation of the vessels as the terminal nervous network remains and is reactive. This, of course, is the opinion of Stöhr, previously reviewed. The author advocated administration of thyroid extract and vitamin B_1 in the postoperative period for improving end results.

The effect of sympathectomy on the vasa vasorum of the rat was reported by Griffith.[166] He injected carbon particles into the blood stream and found a greater number of these particles in the sympathectomized vessels; from this he concluded that the nourishment of the vessel wall improves after sympathectomy.

Lewis[62] reemphasized his belief that the local fault in the vessels of patients suffering from Raynaud's disease is the decisive factor determining end results. He examined 6 unselected patients shortly after preganglionic sympathectomy for Raynaud's disease. In 3 patients attacks occurred spontaneously or could be produced, indicating that local susceptibility to cold remains; the structural damage to the digital vessels seems to determine the failure to abolish all symptoms.

This work of Lewis, together with evidence accumulating elsewhere,[167] is in opposition to the view again strongly expressed by Smithwick[168] that a preganglionic sympathectomy for the upper extremity is the operation of choice for Raynaud's disease. In our experience an extremity in which complete sympathetic denervation has been accomplished, as indicated by cessation of sweating, shows a smaller number of recurrences than the one in which the important first white ramus has been preserved. The controversy regarding preganglionic versus postganglionic sympathectomy still continues and will finally be solved by studying comparable cases over several years.

A highly stimulating study of pain in a fantom limb by Livingston[169] is directed against the often annoying and sometimes permanently intractable pain in an amputated limb projected distally to the level of amputation. He advocated the injection of procaine hydrochloride into the sympathetic ganglions, which curiously enough abolishes this pain for several months or years and may then have to be repeated. The author expressed a doubt that an interruption of afferent sensory fibers

166. Griffith, J. A.: The Effect of Sympathectomy on the Vasa Vasorum of the Rat, Am. J. Path. **20**:984, 1938.

167. de Takáts, G.: Analysis of Results Following Sympathectomy for Peripheral Vascular Disease, Am. J. Surg., to be published.

168. Smithwick, R. H.: Immediate Effects and Late Results of Sympathetic Denervation of the Upper Extremity by Preganglionic Section, read before the American Heart Association, St. Louis, May 13, 1939.

169. Livingston, W. K.: Fantom Limb Pain, Arch. Surg. **37**:353 (Sept.) 1938.

is accomplished but held that a reflex arc is broken, which may not reestablish itself after the temporary block with procaine. This line of thought is similar to that expressed by our group in regard to "reflex dystrophies" following slight injuries or infections.[153]

Lumbosacral sympathectomy was performed on 5 patients suffering from diabetic gangrene.[170] The authors expressed the opinion that the operation delayed the process of gangrene, limited the infection and reduced the claudication. How this was brought about and how the patients were selected are not apparent. It is not all clear why a process which is predominantly an obliteration of the middle-sized and terminal arteries would be benefited by sympathectomy. Should a vasopastic element be present, heat and rest in bed would effectively reduce it.

In 6 patients suffering from hyperhidrosis White [171] obtained excellent results by preganglionic sympathectomy. Only 1 patient had a paravertebral injection of alcohol, but as such treatment is occasionally followed by intercostal neuritis, the author expressed a preference for surgical removal of the upper thoracic chain with preservation of the first white ramus. Thus Horner's syndrome is avoided.

Our unpublished observations have made us cautious in advocating sympathectomy for hyperhidrosis unless it is strictly limited to the extremities. In 1 patient all the extremities were subjected to sympathectomy, but the sweating in the nondenervated areas became almost unbearable. Psychotherapy, tried in 1 case, resulted in no benefit. Hyperhidrosis without vascular spasm deserves further intensive study.

Telford [172] stated that while the patchy type of scleroderma may be stopped by sympathectomy, the sclerodactylia seen in the late stages of Raynaud's disease is not affected by the operation. In cases of hyperhidrosis the results were excellent. In 27 cases of poliomyelitis and 40 cases of erythrocyanosis, a condition more frequent in England, the results were very good. The author expressed the belief that sympathectomy has a definite place in well selected cases of skin disease.

SURGICAL TREATMENT OF HYPERTENSION

Smithwick [173] expressed succinctly the present status in this field as follows: "The surgical attack on hypertension must still be regarded

170. Chabanier, H.; Gaume, P., and Lobo-Onell, C.: De la sympathectomie lombo-sacrée dans les artérities diabétiques des membres inférieurs, Presse méd. **46**:1161 (July 27) 1938.

171. White, J. C.: Hyperhydrosis of Nervous Origin and Its Treatment by Sympathectomy, New England J. Med. **220**:181, 1939.

172. Telford, E. D.: Some Experiences of Sympathectomy in Diseases of the Skin, Brit. J. Dermat. **50**:637, 1938.

173. Smithwick, R. H.: Surgery of the Sympathetic Nervous System, New England J. Med. **220**:475, 1939.

as in the experimental stage. It takes years of trial and error to determine the most effective way of denervating any portion of the vascular bed. The lack of uniformity of results in identical cases leads one to suspect that this has not yet been accomplished in regard to the splanchnic bed."

This statement expresses the quandary in which every surgeon who is familiar with the results of sympathectomies for hypertension finds himself. If he has followed his patients carefully, he has seen a number of objective and a smaller number of subjective failures. He has occasionally seen a remarkable result, perhaps in a patient in whom he least expected it. All the preoperative tests notwithstanding, the results of the surgical procedure are yet unpredictable. That section of the splanchnic nerve or denervation of the adrenal gland does not exert any influence through denervation of the adrenal medulla was pointed out by Hermann,[174] who stated that in the dog the adrenal medulla does not change morphologically nor does it lose its power to secrete its specific hormone or to react to electric or to pharmacologic stimuli. He expressed the opinion that the gland can escape the control of the central nervous system without losing the capacity to produce and discharge epinephrine; this should be taken into account when operations for hypertension or diabetes are under consideration.

Craig [175] restated the indications, preoperative tests and results of subdiaphragmatic section of the splanchnic nerve with reference to 158 patients treated at the Mayo Clinic. All patients are divided into four groups, as discussed elsewhere in this review. The first group requires no surgical treatment, and the second and third groups should be considered for surgical treatment, whereas in the fourth group the findings constitute a contraindication. In general, 70 per cent of the patients operated on were benefited.

C. H. Moore [176] reported on 22 patients in whom section of the splanchnic nerve had been performed and who had been followed up for a period of more than thirty months; 90 per cent of these showed an immediate postoperative drop in blood pressure. The reduction of blood pressure was maintained for over a year in 45 per cent. Symptomatic improvement, without a fall in blood pressure, was noted in 27 per cent. No improvement other than some immediate relief was registered in 27 per cent. In 9 per cent not even an immediate drop was noted. One patient (4 per cent) died.

174. Hermann, H.: Le comportement de la glande médullosurrénale énervée (données expérimentales), Presse méd. **46**:1554 (Oct. 22) 1938.

175. Craig, W. M.: Essential Hypertension: Selection of Cases and Results Obtained by Subdiaphragmatic Extensive Sympathectomy, Surgery **4**:502 (Oct.) 1938.

176. Moore, C. H.: Surgical Treatment of Hypertension, South. Surgeon **7**:353 (Aug.) 1938.

Such reports as these are urgently needed. One cannot brush aside these operations with the remark that they constitute a form of psychotherapy. With 72 per cent of the patients showing either a fall in blood pressure or no fall but definite symptomatic improvement, one feels encouraged to continue in spite of many failures.

That exclusion of the splanchnic bed seriously interferes with a reflex pressor mechanism is clearly illustrated by the observations of Moore and Allen,[177] who found that following section of the splanchnic nerve pressure on the carotid sinus results in significant decreases of blood pressure associated with marked bradycardia. Just how long this sensitivity of the carotid sinus persists is not clear. It is known that the postural hypotension resulting from this operation is temporary.

The work of Goldblatt on experimental renal hypertension is beginning to exert its influence on the clinical literature. Thus Butler[178] reported 2 children with pyelonephritis in whom the concomitant hypertension was cured by nephrectomy. He emphasized the difficulty of differentiating between primary vascular and secondary renal hypertension. The two children had hypertension before any renal damage became evident, just as did the dogs Goldblatt described. Clinical findings very similar to those of experimental hypertension were reported by Barney and Suby,[179] of the Massachusetts General Hospital, Boston, in a patient with unilateral renal disease and arterial hypertension, who was apparently cured following nephrectomy. Since this patient suffering from unilateral renal disease associated with, and probably causing, arterial hypertension was cured for twenty-one months by nephrectomy, Barney and Suby suggested the importance of carefully studying and following up patients with unilateral renal disease, especially from the point of view of hypertension, both before and after operation. The results of their studies are as follows:

Since 1911, at the Massachusetts General Hospital there have been 305 patients with unilateral renal disease, on 224 of whom unilateral nephrectomy was performed. Seventy-six (25 per cent) had hypertension, with a preoperative systolic blood pressure of at least 140 mm. of mercury.

Only 15 of these 244 patients could be followed with subsequent readings of blood pressure. Of these patients, all of whom were followed for four months to nine years after operation, 10 (67 per cent) showed an average drop in systolic pressure of 40 mm., as compared with the preoperative level.

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177. Moore, F. H., and Allen, E. V.: Vascular Clinics: Carotid Sinus and Hypertension, Proc. Staff Meet., Mayo Clin. **13**:747 (Nov. 23) 1938.

178. Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, J. Clin. Investigation **16**:889 (Nov.) 1937.

179. Barney, J. D., and Suby, H. I.: Unilateral Renal Disease with Arterial Hypertension, New England J. Med. **220**:744 (May 4) 1939.

Chabanier and his associates [180] reported on surgical procedures in 49 patients with "nephroangiosclerosis." They discussed benign angiosclerosis, which is pure arteriosclerosis and is only seldom seen below the age of 60. They also discussed malignant nephrosclerosis, in which endarteritis proliferans is a feature. This is a disease of the young. Histologically, increase in elastic tissue and hypertrophy of the muscular wall are evident. In 29 of the 43 patients with malignant nephrosclerosis no arteriosclerotic element was detectable. This condition may start as symptomatic hypertension, but later, when tubules, glomeruli and interstitial tissues become involved, a nephritic picture develops, with appearance of albumin, casts and red cells. After this the average duration of life is five years. Hypertension with nephritis, then, may be due to malignant nephrosclerosis with glomerular manifestations or to chronic diffuse glomerulonephritis with secondary vascular changes.

The value of such findings lies in the fact that the diagnoses were based on the results of renal biopsies made during the operative procedures. The following surgical measures were used: 1. For the patient in a terminal stage, with marked renal insufficiency or cardiac decompensation, one kidney was decapsulated; if the patient improved, the other kidney was decapsulated, with section of the splanchnic nerve or renal denervation. 2. For the patient not in a terminal stage, section of the splanchnic nerve, adrenal denervation, decapsulation or removal of the aorticorenal ganglion has been done. The authors now favor combination of the last two methods.

The results of these procedures are given in too vague terms. The pressure arises again in most instances, but the symptoms of headache, palpitation and dizziness are relieved. This work would be quite inconclusive but for the excellent correlation of clinical pictures with the results of renal biopsies. In our clinic the results of such biopsies have now been studied for several years. It seems easier, however, to remove a small section of the kidney than to get a conclusive histologic report on it, as surgical specimens of this sort are rare. It will be necessary for such kidneys to be studied with special staining methods by men devoting themselves to this field.

Another attempt to revascularize the kidney in hypertension was reported by Abrami, Iselin and Wallick,[181] who made unilateral omental transplants in 1 patient with chronic glomerulonephritis and 1 patient

180. Chabanier, H.; Gaume, P., and Lobo-Onell, C.: Vue d'ensemble sur les résultats d'interventions pratiquées dans 49 cas de néphroangiosclérose, Presse méd. **46**:1818 (Dec. 10) 1938.

181. Abrami, P.; Iselin, M., and Wallick, R.: Essai de traitement de l'hypertension artérielle d'origine rénale par la revascularisation chirurgicale du rein, Presse méd. **47**:137 (Jan. 28) 1939.

with malignant nephrosclerosis. No clinical effect was noted in either patient after a few months. The authors expressed the belief that they were the first ones to have performed these operations, but at our clinic 3 such patients have been followed for several years. Essentially negative results are to be published shortly.

The effects of nonspecific operations on essential hypertension were studied by Volini and Flaxman.[182] They presented data on 27 patients who had had major operations such as cholecystectomy, hysterectomy and prostatectomy. They stated that all patients were relieved of headaches, pain in the chest, dizziness and fatigue, regardless of the operation performed. The duration of the symptom-free stage varied from four months to nine years, averaging three and a half years. The authors expressed the opinion that the results were better than those of any of the specific operations reported in cases of essential hypertension. They expressed a doubt whether surgical methods for the treatment of essential hypertension are ever justified.

An analysis of the tabulated results, however, does not reveal (1) the frequency of follow-up or (2) the extent to which cardiac decompensation and coronary insufficiency were the real factors in the fall of blood pressure. It is not clear how many symptoms these patients had referable to hypertension.

That rest in bed, anesthesia, loss of blood and psychic effect are all conducive to a lowering of blood pressure is obvious, but that bilateral herniotomy, for instance, done in a patient with a preoperative blood pressure of 250 systolic and 160 diastolic would result in freedom from symptoms for eight months is rather remarkable; some of the operations, such as prostatectomy with urinary obstruction and oophorectomy, may, of course, have a direct effect on hypertension.

AMPUTATION FOR VASCULAR DISEASE

Veal[183] reported on 110 patients who had amputations for arteriosclerotic gangrene, excluding patients with diabetes. With better preoperative care, earlier amputation and earlier mobilization, the mortality rate of 39 per cent dropped to 28.8 per cent. Pneumonia, shock and cardiac failure were the most frequent causes of death. Considering the type of material (Charity Hospital, New Orleans) the newer mortality rate is excellent.

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182. Volini, J. F., and Flaxman, N.: The Effect of Nonspecific Operations on Essential Hypertension, J. A. M. A. **112**:2126 (May 27) 1939.

183. Veal, J. R.: Factors in the Mortality Rate of Arteriosclerotic Gangrene: Comparative Study of 214 Cases of Surgical Intervention, J. A. M. A. **110**:785 (March 12) 1938.

Taylor,[184] of the University of Indiana, also reported on efforts to reduce the high mortality from amputations. When the primary consideration is the saving of the patient's life, a simple guillotine amputation is indicated. Diabetes increases the mortality; in 77 amputations on 65 patients with this condition there were 30 deaths, a mortality of 38 per cent in regard to operations and 46 per cent in regard to patients. Among patients who had cellulitis, the mortality was 60 per cent. In the absence of diabetes 37 amputations resulted in 10 deaths, giving 27 per cent mortality for amputations and 35 per cent for patients.

The important point stressed by the author is the futility and danger of attempting to suture fascial layers over the bone. A loose closure of skin gave 27.7 per cent mortality; a primary fascial suture, 43.7 per cent. The first amputation can be readily made through the knee joint, with a secondary amputation above it when the infection has subsided.

It has been realized for some time that hospitals having an amputation service, in which all amputations are concentrated, show a decreasing percentage of mortality. Amputations properly performed are delicate surgical procedures. The determination of indications and of the proper level and the decision in regard to a one or a two stage amputation require an amount of experience which the casual operator hardly possesses. The quick rehabilitation of a crippled patient by means of temporary and permanent artificial limbs is an added duty of the surgeon.

During the last two years Allen has contributed an interesting series of experiments dealing with the beneficial effect of refrigeration of limbs deprived of their circulation. In the latest report[185] he suggested refrigeration of limbs that are to be amputated for the relief of pain, to enable the surgeon to apply a tourniquet and thus eliminate absorption. The author based his suggestions on animal experiments and stated that the exact clinical benefits or limitations await trial. It is an interesting thought which should be approached with considerable caution.

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184. Taylor, F. W.: Amputation Stump of Arteriosclerotic Gangrene, Surg., Gynec. & Obst. **67**:114 (July) 1938.

185. Allen, F. M.: Experiments Concerning Ligation and Refrigeration in Relation to Local Intoxication and Infection, Surg., Gynec. & Obst. **68**:1047 (June) 1939.

News and Comment

Internships Open in California.—The California State Personnel Board is seeking persons well qualified for employment as student intern and senior intern. There is no residence requirement for examination, and no written test will be given. Applicants will be rated on education, experience and scholastic record. Applications may be filed with the executive officer, State of California Personnel Board, 1025 P Street, Sacramento, at any time during the current year and will be rated immediately. If a candidate's qualifications are acceptable, his name will be placed on the list of those eligible for employment in accordance with his rating.

Bulletin of the Société d'Endocrinologie.—The *Annales d'endocrinologie*, the official bulletin of the Société d'Endocrinologie was established this year, the first number being published in March. The editorial committee consists of Guy LaRoche (editor in chief), R. Courrier, J. DeLarue, Justin Besançon, E. May, L. Portes, C. Richet, P. Sainton, H. Simonnet and H. Stevenin.

Book Reviews

William B. Wherry, Bacteriologist. By Martin Fischer. Price, $4. Pp. 293. Springfield, Ill.: Charles C. Thomas, Publisher, 1938.

When Martin Fischer elected to write the biography of his friend, associate and contemporary William B. Wherry, he added another quiet chapter to modern medical history. It is a pity that the layman, so obviously hungry for information about the progress of medicine and the biologic sciences, should not be fed his facts through the pleasing medium of biography rather than the less reliable medium of autobiographic confidences. No man, no matter how excellent his intentions, can properly weigh the human values in his memories of himself; it is to the distinct advantage of society when some Boswell is available who is willing and eager to write the story as he knows it.

Wherry was born in India in 1874, the son of American missionaries. His parents were well educated and poor. When William was 14 years old the parents moved back to the homeland to provide an education for their children. Rev. Elwood Wherry resigned from his missionary work in foreign fields and obtained the promise of a position for himself with the American Tract Society. He settled in River Forest, Ill., just west of Chicago, and built a home on Ashland Avenue, which was for many years to function as the only permanent postoffice address of an always widely scattered family. Young William tramped the still unsettled west side districts of Chicago with a notebook and pencil; the "seeing eye" of the innate scientist was already his.

At 19 he entered Washington and Jefferson College, his father's Alma Mater, and in four years, on an unbelievably slim purse, he received his degree of Bachelor of Arts. In the autumn of 1897 he entered Rush Medical College, where for the first time he was to meet his future biographer. The days of his attendance were the heydays of Rush, the days of its great teachers, dedicated "to the common purpose of producing capable doctors—men able to meet a medical situation, whatever its nature, wherever found." Fischer writes of his and Wherry's school days there with comforting nostalgia; it is too easy to sneer back at the past from the heights of one's own achievements.

During his second year Wherry knocked and gained admittance at the laboratory of pathology, presided over by Prof. Ludvig Hektoen. Hektoen had been taught the ultimate in morphologic pathology, but he taught his pupils something contrary. Morphology was dead, he said. Progress lay in bacteriology, in immunology, in experimental medicine and in dynamic concepts of disease. Here in Hektoen's laboratory Wherry met E. R. Le Count and G. H. Weaver, H. Gideon Wells and E. C. Rosenow, D. J. Davis, Peter Bassoe, Brown Pusey, H. T. Ricketts, R. T. Woodyatt, Alice Hamilton and Martin Fischer. It is difficult to picture a happier association than that which must have been experienced between this dynamic leader and his alert disciples.

Wherry got his degree of Doctor of Medicine from Rush in 1901 and went from medical school to Dr. E. O. Jordan's laboratory on the University of Chicago campus. There he earned his first salary, $1,000 a year, established a firm friendship with Dr. Jordan and met as a pupil Marie Eleanor Nast, of Cincinnati, whom he was later to marry. Through Dr. Jordan he became interested in tropical disease, and because of Miss Nast, in the hope of eventually being able to support a wife, he applied for and won a research position in the government laboratories in the Philippine Islands. In Manila he worked with Paul G. Woolley, of Johns Hopkins University, with whom he was later to be associated in Cincinnati. This

period was rich in experience and filled with valuable results, but it brought with it no financial security, and Wherry returned to the mainland after three years in the Philippines with his pockets still empty.

The story of the next few years is the chronicle of almost all well trained young scientists who ask only a living and a laboratory from life. The tragedy lies in the fact that the living they demand is so pitifully small and so difficult to acquire. Wherry, perhaps, was more fortunate than many. At any rate, he progressed. He got an assignment in Anaconda, Mont., to investigate the cause of the mysterious deaths of countless cattle whose owners were suing the Copper Mining Company for responsibility. When his investigations in Montana were completed he was invited to Oakland, Calif., as professor of bacteriology in the medical school there. Martin Fischer was in Oakland and instrumental in Wherry's appointment. In December 1906 Wherry married Marie Eleanor Nast, who now had the degree of Doctor of Medicine from Johns Hopkins University, and the two went from Cincinnati to Oakland, where both medical Wherrys had teaching appointments in the medical school. William B. Wherry, the professor of bacteriology, had been there for only four months when he was summoned to San Francisco. There was bubonic plague on the Pacific Coast, and the bay cities were in quarantine. Wherry was asked to come to San Francisco to discover its source. He organized a fight against San Francisco's rats, inspected and performed autopsies on the human dead, surveyed about a million and a half properties, reduced morbidity and mortality, brought a lift of the quarantine—and was dismissed. The city had gone far enough, but Wherry was not satisfied with the results. Plague broke out in Seattle and was discovered inland in California, away from the water fronts. Finally, it was found in the ground squirrels which infested the western states. Wherry's conclusion that bubonic plague was endemic on the West Coast, which should be protected against itself rather than from the rats on incoming ships, was serious. It was more difficult to wage war against the thousands of independent squirrel hunters who persisted in the pleasures of individualism than against the helpless rats in San Francisco's sewers.

In 1909, on nomination of Paul G. Woolley, who was already installed at the University of Cincinnati, Wherry was invited to become the bacteriologist in the department of pathology at the reorganized medical school there. The salary offered was $1,800 a year. The business of being only an assistant professor did not disturb him, but he wanted time away from his teaching for independent research and stipulated for financial support equal to what he was receiving at Oakland, Calif. Cincinnati offered $2,400, and Wherry accepted. During the next year Martin Fischer joined the staff. Wherry was happy. He wrote of the situation to his mother, who replied: "It must be very nice indeed for so many of you young fellow-student doctors to be working in the same place."

Wherry had arrived. He was 35 years old; he had a wife and a growing family and a salary of $2,400 a year. And he had a teaching position which he enjoyed and a laboratory which he could use. His work on tularemia and his studies on oxygen tension were done there. As his name became more widely known and his work more publicized, he had opportunities to go elsewhere. But his interests and loyalties were with the school in whose reorganization he had played an important part.

He died in Cincinnati in 1936 at a little less than 62 years of age. He had led a pleasant as well as a valuable life. His early attempts with the naturalist's notebook in the woods west of Chicago had developed into a taste for sketching and later to successful experiments with brush and canvas. He had played with as great a zest as he had worked. He maintained throughout his life his friendships and old loyalties and found time for new ones. The *Cincinnati Post* editorialized his life on the day of his death: "He died here Sunday, unknown to the general public. But that is as he wanted it. His scientific work was for use, not for the spotlight."

Practice of Medicine. By Jonathan C. Meakins, M.D., LL.D. Price, $12.50. Pp. 1413, with 521 illustrations. St. Louis: C. V. Mosby Company, 1938.

The appearance of a new edition of a textbook about two years after the original edition was presented to the medical public indicates that the book was favorably received by the profession. It can be well understood why this is the case. Meakins has written a book on the practice of medicine which in the first edition had many things to commend it and a few features that might be criticized. In the second edition some changes, which on more mature consideration the author thought advisable, have been made, but they are few and far between. The original edition was so comprehensive and so well done that few alterations were necessary.

A feature thought most commendable in the first edition has been continued of course in the second, namely, a discussion of the symptoms and symptomatology of disease in the various systems of the body.

The explanation of the mechanism of production of these signs and the pathologic physiology concerned therewith is well worth the price of the book. For example, the physiologic disturbance resulting in dyspnea is excellently detailed and lucidly explained. On the other hand, I do not think it is necessary to incorporate a large number of reproductions of roentgenograms, which take up much space and make the book heavy and unwieldy. Most of the roentgen plates are good, but with few exceptions they add little to the value of the book. This feature has evidently been criticized, for in the preface to the second edition Meakins says that the depiction of rare conditions is an important feature of the book. Such illustrations may appear properly in a system or encyclopedia of medicine, but it hardly seems necessary to burden a tome which is obviously intended for a textbook with colored reproductions of unusual lesions, which frequently are nothing more than pathologic curiosities and which in many instances could be diagnosed at a glance.

In the preface, certain additions made in the second edition are specifically mentioned, namely, discussions of acute laryngotracheobronchitis, tuberculous tracheitis, "cysts" of the lung, Friedländer's bacillus pneumonia, lipoid pneumonia, monocytic leukemia, nutritional edema, protamine zinc insulin, experimental nephritis, vascular renal failure, congenital aplasia of the kidney, uremic state, sulfanilamide therapy, lymphogranulomatosis inguinalis, epidemic pleurodynia and Cannabis indica intoxication. With these additions the book seems to be a complete textbook. A study of the index and reference here and there to the text shows that little seems to be omitted or neglected which might be of interest and value to the practitioner or student.

Sulfanilamide Therapy of Bacterial Infections. By Ralph R. Mellon, M.D.; Paul Gross, M.D., and Frank B. Cooper, of the Institute of Pathology, Western Pennsylvania Hospital, Pittsburgh. Price, $4. Pp. 398, with tables and graphs. Springfield, Ill.: Charles C. Thomas, Publisher, 1938.

Advances in the knowledge of the types, actions, uses and chemotherapeutic implications of the sulfanilamide compounds have been so rapid that the need for a comprehensive summary of the facts has become very real. This need has been well met by the authors of this book in their first section, which comprises a review, with a bibliography, of all the literature on the sulfonamide group of drugs. This review should be immensely useful to both clinicians and laboratory workers in various phases of chemotherapeutic research. The clinician will be particularly interested in the chapters devoted to the indications, routes of administration, schemes of dosage, toxic manifestations and results of sulfanilamide therapy in various infections.

The second section of the book deals with the authors' experiments on the bacteriostatic action of sulfanilamide and emphasizes the great discrepancies between the in vitro and the in vivo effects of the drug. Some possible factors

producing this difference—variations in the dose of the infecting organism, the virulence of the particular strain of the organism and the fitness or resistance of the host—are discussed.

The third section details the authors' experiments designed to explain these differences. They show that, while physiologic solution of sodium chloride and blood serum containing dilutions of sulfanilamide in concentrations as high as 1:4,000 have only slight bacteriostatic effects on small and moderate-sized inoculums of several strains of streptococci and colon bacilli, the addition of small amounts of physiologic solution of sodium chloride to human serum produces virtual sterilization of such inoculums. This effect far exceeds a simple summation of the bacteriostatic effects of salt solution and human serum taken singly. The phenomenon is termed by the authors potentiation and explains the differences, at least in part, between the in vivo and the in vitro actions of sulfanilamide. It offers a particularly tempting explanation of the great efficacy of sulfanilamide in low dilution in the urine against infections of the urinary tract due to Escherichia coli.

The remaining section of the book is devoted to a consideration of biologic controls in chemotherapeutic work. Addenda are given which review the articles published while the work was in press.

The book is nicely planned and is printed in large, easily read type. It can be recommended to workers in all branches of medicine.

Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance: A Contribution to the Structure and Function of the Hypothalamico-Hypophyseal System. By Charles Fisher, Ph.D.; W. R. Ingram, Ph.D., and S. W. Ranson, Ph.D., M.D. Price, $5. Pp. 212, with 71 illustrations. Ann Arbor, Mich.: Edwards Brothers, Inc., 1938.

This monograph is concerned with the nervous and hormonal factors involved in the regulation of water balance and especially with the great increase in water exchange which characterizes the disease known as diabetes insipidus. The investigations were carried out in the Institute of Neurology of Northwestern University Medical School during the past six years. Although most of the facts presented have been published by the authors in various periodicals, it is highly pleasing to find them correlated and collected into one volume.

The principal method of study was the production of discrete lesions in various parts of the hypothalamus with the Horsley-Clarke stereotaxic instrument. Diabetes insipidus was produced in 85 cats and 2 monkeys. Among the final conclusions of the investigators are that the neural lobe of the hypophysis is an endocrine gland which plays an antidiuretic role in renal water balance and that diabetes insipidus is essentially a hypophysial deficiency syndrome caused by a diminution or by absence of the antidiuretic hormone of the neural lobe when the latter is extirpated or becomes atrophic secondary to interruption of the supraoptico-hypophysial tracts.

Essentials of Pathology. By Lawrence W. Smith and Edwin S. Gault. Price, $9. Pp. 886, with 679 illustrations (160 plates). New York: D. Appleton-Century Company, Inc., 1938.

This handsome volume represents an attempt to teach pathology by emphasis on the case history method. After short introductory paragraphs on the various conditions, a case history with a pathologic report is added. Some case reports are accompanied by illustrations. While this method is worthy of commendation, specific case studies are usually furnished in the practical part of any course in pathology and the textbook perhaps should deal with the subject in a more reflective, general and philosophic manner. However, the book is of interest, and the illustrations are especially good.